Notice/Disclaimer: The clinical information contained herein is provided for the express purpose of aiding the Pharmacy and Therapeutics ("P&T") Committee members in reviewing medications for inclusion in or exclusion from the Virginia Preferred Drug List. This information is not intended nor should it be used as a substitute for the expertise, skill, and judgment of physicians, pharmacists, or other healthcare professionals. The absence of a warning for any given drug or drug combination should not be construed to indicate that the drug or drug combination is safe, appropriate or effective for any given patient. This information is intended to supplement the knowledge and additional resources available to the P&T Committee members and should not be considered the sole criteria used by the P&T Committee in deciding what medications will be included or excluded from the Virginia Preferred Drug List.

Virginia Pharmacy and Therapeutics Committee Clinical Class Reviews
September 3, 2003

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Clinical Trial Acronyms i

ACE Inhibitors			
Characteristic	**Zestril, Prinivil (Lisinopril)**	**Accupril (Quinapril)**	**Monopril (Fosinopril)**
Pharmacology	Angiotensin-Converting Enzyme (ACE) Inhibitors (ACEIs) are comounds that appear to act primarily by suppression of the renin-angiotensin-aldosterone system. Renin (synthesized in the kidneys) is released into the circulation where it acts on angiotensinogen to produce angiotensin I, a relatively inactive decapeptide, which is then converted by ACE to angiotensin II, a potent endogenous vasoconstrictor. Angiotensin II stimulates aldosterone secretion from the adrenal cortex, contributing to sodium and fluid retention. ACEIs block the conversion of angiotensin I to angiotensin II by inhibiting ACE; they do not alter pressor responses to other agents. ACEIs may also inhibit local angiotensin II production at vascular and renal sites and attenuate the release of catecholamines from adrenergic nerve endings.		
Manufacturer	Multiple generics available	Parke-Davis	Bristol-Meyers Squibb
Date of FDA approval	Available generically	November, 1991	MAY 16, 1991
Generic available?	Yes	No; On June 4, 2003 the FDA gave Teva the 180 day exclusive approval to market a generic version of Parke-Davis' antihypertensive drug Accupril (quinapril hydrochloride). However, there are multiple patents that further protect the drug, including a "stabilized" formulation patent that protects the compound until 2007. The strength of these patents may prevent generic manufacturer if litigation ensues.	No; On July 11, 2003 the FDA gave tentative approval for Teva to make a generic version of Monopril. The approval hinges on the outcome of litigation with Monopril maker Bristol-Myers Squibb and Teva. Teva is currently involved in paragraph IV litigation with Bristol-Myers Squibb concerning this product. A trial at the District Court was completed in May and a decision has not yet been rendered, thus preventing availability of the generic.
Dosage forms / route of admin.	Lisinopril & Zestril Tablets: 2.5, 5, 10, 20, 30, 40 mg Prinivil Tablets: 2.5, 5, 10, 20, 40 mg	Accupril Tablets: 5, 10, 20, 40 mg	Monopril Tablets: 10, 20, 40 mg
	WITH HCTZ: Lisinopril/HCTZ Prinzide, Zestoretic: 10/12.5, 20/12.5, 20/25mg (available generically)	**WITH HCTZ:** Quinapril/HCTZ Accuretic: 10/12.5. 20/12.5, 20/25 mg tabs	**WITH HCTZ:** Fosinopril/HCTZ Monopril HCT: 10/12.5, 20/12.5 mg tabs
Dosing Frequency	QD	QD or BID	QD or BID

ACE Inhibitors			
Characteristic	**Zestril, Prinivil (Lisinopril)**	**Accupril (Quinapril)**	**Monopril (Fosinopril)**
General Dosing Guidelines	**Hypertension:** ▪ Initial: 10 mg QD. Usual QD range is 20 – 40 mg/day. ▪ Doses ≤80 mg have been used but do not appear to give a greater effect. ▪ Renal function impairment: 10 mg QD with Ccr > 30 ml/min, 5 mg QD with Ccr ≥ 10 to ≤ 30 ml/min, 2.5 mg QD in dialysis patients (administer post-dialysis), max of 40 mg QD **Heart failure**: ▪ Initial: 5 mg QD. ▪ The usual effective dosage range is 5-20 mg/day as QD. ▪ In patients with heart failure who have hyponatremia or moderate-to-severe renal impairment (Ccr ≤ 30 ml/min), initiate at a dose of 2.5 mg QD. **Acute MI:** ▪ Initial: 5 mg, followed by 5 mg after 24 hrs, 10 mg after 48 hrs, and then 10 mg QD x 6 wks. Pts with a low SBP (≤ 120 mmHg) when tx is started or during the first 3 days after the MI should be given a 2.5 mg dose. If SBP is ≤ 100 mmHg, 2.5-5 mg QD.	**Hypertension** ▪ Initial: 10 or 20 mg QD for patients not on diuretics. Adjustments can be made at ≥ 2 wks ▪ Maintenance: 20, 40, or 80 mg/day QD or BID. ▪ Elderly (≥65 yoa): 10 mg QD. ▪ Renal function impairment: Initial 10 mg QD with Ccr > 60 ml/min, 5 mg with Ccr 30-60 ml/min, or 2.5 mg with Ccr 10-30 ml/min. Insufficient data to recommend when Ccr < 10 ml/min. **Heart failure** ▪ Indicated as adjunctive therapy. Starting dose is 5 mg BID. Titrate to 20-40 mg daily given in 2 equally divided doses. Adjustments can be made at weekly intervals. ▪ Renal impairment or hyponatremia, initial dose is 5 mg with Ccr > 30 ml/min or 2.5 mg with Ccr 10-30 ml/min. If tolerated, quinapril may be given the following day as BID. Insufficient data to recommend when Ccr < 10 ml/min.	**Hypertension** ▪ Initial: 10 mg QD. ▪ Maintenance: Usual range needed to maintain a response is 20-40 mg/day, but some patients appear to have a further response to 80 mg. Daily dose can be divided if antihypertensive response diminishes towards the end of the day. **Heart failure** ▪ Starting: 10 mg QD. An initial dose of 5 mg is preferred in heart failure patients with moderate-to-severe renal failure or in those who have been vigorously diuresed. ▪ The usual effective dosage range is 20-40 mg QD, max of 40 mg daily. Dosage increases should be made over several weeks. **NOTE:** [Renal Impairment: Dual routes of elimination, hepatobilliary and renal, allow for usual dosing at any level of renal impairment, even end stage, Ccr < 10ml/min.]
Pediatric Labeling	Safety and efficacy have not been established.		
FDA Labeled Indications	▪ Hypertension ▪ CHF ▪ Acute MI	▪ Hypertension ▪ CHF	▪ Hypertension ▪ CHF

<table>
<tr><th colspan="4">ACE Inhibitors</th></tr>
<tr><th>Characteristic</th><th>Zestril, Prinivil
(Lisinopril)</th><th>Accupril
(Quinapril)</th><th>Monopril
(Fosinopril)</th></tr>
<tr><td>Other studied uses</td><td>▪ Reduces progression of renal disease in normotensive patients with type 2 diabetes (EUCLID Study Group)
▪ Migraine prophylaxis</td><td>▪ Shown to reduce ischemic events after CABG (QUO VADIS Study)</td><td>▪ Monopril had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina than those receiving amlodipine in hypertensive type 2 diabetics (FACET trial).</td></tr>
<tr><td>Contraindications</td><td colspan="3">▪ Angioedema: ACE inhibitor-induced, history of, hereditary or idiopathic.
▪ Hypersensitivity to any ACE inhibitor.
▪ Pregnancy
▪ Renal artery stenosis (solitary kidney or bilateral disease)</td></tr>
<tr><td>Drug interactions</td><td colspan="3">NSAIDs, Probenecid (captopril), Rifampin (enalapril), Allopurinol (captopril), Lithium, Potassium preparations/Potassium-sparing diuretics, Tetracycline (quinapril).</td></tr>
<tr><td rowspan="4">Major AEs / Warnings</td><td colspan="3">▪ First dose syncope, cough, angioedema sinusitis, headache, pharyngitis, vomiting, ALT increase, male sexual dysfunction</td></tr>
<tr><td colspan="3">▪ Pregnancy: Category C (first trimester); Category D (second and third trimester). When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme inhibitors (ACEI's) can cause injury to and even death in the developing fetus. When pregnancy is detected, discontinue the ACE inhibitor as soon as possible.</td></tr>
<tr><td colspan="3">▪ Lactation: Exercise caution. Consider the importance of the drug to the mother as to whether or not to discontinue nursing.</td></tr>
<tr><td colspan="3">▪ Neutropenia/ agranulocytosis, anaphylactic and related reactions, proteinuria, hypotension, renal fxn. Impairment, hepatic fxn. Impairment, hyperkalemia, cough</td></tr>
<tr><td>Pharmacokinetics issues</td><td>▪ Protein binding: not applicable
▪ Affect of food on absorption: none
▪ Active metabolite: none</td><td>▪ Protein binding: about 97%
▪ Affect of food on absorption: reduced by 25-30% with a high fat meal
▪ Prodrug: quinaprilat</td><td>▪ Protein binding: about 99.4%
▪ Affect of food on absorption: slightly reduced
▪ Prodrug: fosinoprilat</td></tr>
<tr><td>Dosage adjustment in key populations</td><td colspan="3">▪ Dosage reduction or discontinuation may be required in those with renal impairment except for Monopril® fosinopril.
▪ Fosinopril: Patients with hepatic impairment may require dosage adjustment No overall difference in safety and /or effectiveness.
▪ Quinapril: Elderly patients may have higher blood levels and AUC of quinaprilat (active metabolite of quinapril). However, decreased renal function may be more relevant than age. Initiate at 10mg/day and titrate to response
▪ Lisinopril: Elderly patients may have higher blood levels and AUC of lisinopril. However, decreased renal function may be more relevant than age.</td></tr>
</table>

ACE Inhibitors			
Characteristic	**Zestril, Prinivil (Lisinopril)**	**Accupril (Quinapril)**	**Monopril (Fosinopril)**
Unique Features / Advantages	▪ Does not require hepatic activation, best choice for patients with severe hepatic dysfunction ▪ Absorption is not affected by food		▪ Does not require dosage adjustment in renal impairment due to duel elimination through renal and hepatobilliary routes.
Pipeline	See last page of Class Review		
Efficacy/ Summary	See last page of Class Review		

ACE Inhibitors			
Characteristic	**Capoten (Captopril)**	**Vasotec (Enalapril)**	**Lotensin (Benazepril)**
Pharmacology	Angiotensin-Converting Enzyme (ACE) Inhibitors (ACEIs) are peptides appearing to act primarily by suppression of the renin-angiotensin-aldosterone system. Renin (synthesized in the kidneys) is released into the circulation where it acts on angiotensinogen to produce angiotensin I, a relatively inactive decapeptide, which is then converted by ACE to angiotensin II, a potent endogenous vasoconstrictor. Angiotensin II stimulates aldosterone secretion from the adrenal cortex, contributing to sodium and fluid retention. ACEIs block the conversion of angiotensin I to angiotensin II by inhibiting ACE; they do not alter pressor responses to other agents. ACEIs may also inhibit local angiotensin II production at vascular and renal sites and attenuate the release of catecholamines from adrenergic nerve endings.		
Manufacturer	Multiple generics available	Multiple generics available	Novartis
Date of FDA Approval	Available generically	Available generically	June 1991
Generic available?	Yes	Yes	No; however, on 2/28/03 Eon Labs became the first company to receive tentative FDA approval for generic Benazepril HCl. Barring any patent extensions and litagation, the brand will lose exclusivity on August 11, 2003.
Dosage forms / route of admin.	Brand & Generic Tablets: 12.5, 25, 50, 100 mg Oral	Brand & Generic Tablets: 2.5, 5, 10, 20 mg Oral	Lotensin Tablets: 5, 10, 20, 40 mg Oral
	WITH HCTZ: Captopril/HCTZ Capozide: 25/25, 50/25, 25/15, 50/15 (available generically)	**AS INJECTABLE:** Enalaprilat: inj. for IV use (1.25 mg/ml) **WITH HCTZ:** Enalapril/HCTZ Vaseretic: 5/12.5, 10/25 mg tabs (available generically)	**WITH HCTZ:** Benazepril/HCTZ Lotensin HCT: 5/6.25, 10/12.5, 20/12.5, 20/25mg
		WITH FELODIPINE: Enalapril/Felodipine Lexxel: 5/2.5, 5/5 mg tabs	**With Amlodipine:** Benazepril/amlodipine Lotral: 10/2.5, 10/5, 20/5, 20/10 mg caps
Dosing Frequency	BID or TID	QD or BID	QD or BID

ACE Inhibitors			
Characteristic	**Capoten (Captopril)**	**Vasotec (Enalapril)**	**Lotensin (Benazepril)**
General Dosing Guidelines	**Hypertension** ▪ Initial: 25 mg BID or TID. ▪ Usual range: 25-150 mg BID or TID. Do not exceed daily dose of 450 mg. Adjustments can be made at 1 to 2 week intervals. ▪ Accelerated or malignant hypertension: Initial: captopril 25 mg BID or TID. Dose until a satisfactory response is obtained or the maximum dose is reached. Adjustments can be made every 24 hours. **Heart failure** ▪ Initial: 6.25-12.5 mg TID. ▪ Most doses are 50-100 mg TID; do not exceed 450 mg/day. Can titrate to usual daily dose over several days. **LVD post-MI** ▪ After a single 6.25-mg dose, initiate at 12.5 mg TID then Ξ to 25 mg TID titrate to a target dose of 50-mg TID. **Diabetic nephropathy** ▪ 25 mg TID. **Renal function impairment** ▪ Reduce initial daily dosage and use smaller increments for titration at 1 to 2 week intervals, then reduce to lowest effective dose.	**Hypertension** ▪ Initial: 5 mg QD. ▪ Usual range: 10-40 mg/day as a single dose or in 2 divided doses. Renal function impairment: Titrate to a maximum dosage of 40 mg/day. Initial dosage of 5 mg/day (Ccr > 30 ml/min); 2.5 mg/day (Ccr ≤ 30 ml/min); and 2.5 mg on the day of dialysis in dialysis patients. **Heart failure (adjunct with diuretic and digitalis)** ▪ Usual dosage is 2.5-20 mg/day given BID; maximum daily dose is 40 mg in divided doses. **Asymptomatic LVD** ▪ 2.5 mg BID, titrated as tolerated to the targeted daily dose of 20 mg in divided doses. **Pediatric HTN:** Initial dose, 0.08 milligrams per kilogram (maximum 5 milligrams) once daily -Usual dose, 0.08 to 0.58 mg/kg/day Maximum dose, 0.58 mg/kg/day (40 milligrams) daily **Renal function impairment or hyponatremia** ▪ Initiate at 2.5 mg/day. The dose may be increased to 2.5 mg BID, then 5 mg BID and higher as needed; maximum 40 mg/day. **IV Enalaprilat: slow IV infusion over at least 5 minutes:** 1.25 mg q6 h. Doses as high as 5 mg q 6hrs have been tolerated for 36 hours. There is inadequate experience with doses > 20 mg/day. Patients have received enalaprilat for as long as 7 days	**Hypertension** ▪ Initial: 10 mg QD. ▪ Usual range: 20 to 40 mg/day QD or 2 equally divided doses. A dose of 80 mg gives an increased response; experience is limited. Total daily doses > 80 mg have not been evaluated. **Renal function impairment** ▪ 5 mg QD in patients with Ccr of < 30 ml/min. Dosage may be titrated upward to a maximum of 40 mg/day.

ACE Inhibitors			
Characteristic	**Capoten (Captopril)**	**Vasotec (Enalapril)**	**Lotensin (Benazepril)**
Pediatric Labeling	▪ Safety and efficacy have not been established	▪ Yes: Pediatric labeling as above	▪ Safety and efficacy have not been established
FDA Labeled Indications	Generic Captopril ▪ Hypertension ▪ CHF ▪ LVD post-AMI Capoten ▪ Hypertension ▪ CHF ▪ LVD post-AMI ▪ Diabetic Nephropathy	▪ Hypertension ▪ CHF ▪ Asymptomatic LVD	▪ Hypertension
Other studied uses	Captopril ▪ Management of hypertensive crises ▪ Severe childhood hypertension ▪ Rheumatoid arthritis ▪ Diagnosis of anatomic renal artery stenosis ("captopril test") ▪ Hypertension related to scleroderma renal crisis ▪ Diagnosis of renovascular hypertension in select patients ▪ Diagnosis of primary aldosteronism ▪ Enhance sensitivity and specificity of renal scintigraphy ▪ Idiopathic edema ▪ Bartter's syndrome (improves potassium metabolism and corrects hypokalemia) ▪ Raynaud's syndrome (symptomatic relief)	Enalapril ▪ Diabetic nephropathy Enalaprilat IV ▪ Hypertensive emergencies	▪ Prevention of progression of nondiabetic nephropathy (AIPRI trial) ▪ Heart Failure (The Benazepril Heart Failure Study Group).

ACE Inhibitors			
Characteristic	**Capoten (Captopril)**	**Vasotec (Enalapril)**	**Lotensin (Benazepril)**
Contraindications	Angioedema: ACE inhibitor-induced, history of, hereditary or idiopathic. Hypersensitivity to any ACE inhibitor, pregnancy Renal artery stenosis (solitary kidney or bilateral disease)		
Drug interactions	NSAIDs, Probenecid (captopril), Rifampin (enalapril), Allopurinol (captopril), Lithium, Potassium preparations/Potassium-sparing diuretics, Tetracycline (quinapril).		
Major AEs / Warnings	▪ First dose syncope, cough, angioedema sinusitis, headache, pharyngitis, vomiting, ALT increase, male sexual dysfunction ▪ Pregnancy: Category C (first trimester); Category D (second and third trimester). When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme inhibitors (ACEI's) can cause injury to and even death in the developing fetus. When pregnancy is detected, discontinue the ACE inhibitor as soon as possible. ▪ Lactation: Exercise caution. Consider the importance of the drug to the mother as to whether or not to discontinue nursing. ▪ Neutropenia/agranulocytosis, anaphylactic and related reactions, proteinuria, hypotension, renal function impairment, hepatic function impairment, hyperkalemia, cough		
Pharmacokinetics issues	▪ Protein binding: about 25-30% ▪ Affect of food on absorption: reduced ▪ Active metabolite: none	▪ Protein binding: no data ▪ Affect of food on absorption: none ▪ Prodrug: Enalaprilat	▪ Protein binding: about 97% for parent drug; about 95% for active metabolite ▪ Affect of food on absorption: slightly reduced ▪ Prodrug: benazeprilat
Dosage adjustment in key populations	▪ Dosage reduction or discontinuation may be required in those with renal impairment. ▪ Consideration of dosage reduction in the elderly may be more related to reduction in renal function that age itself.		
Unique Features / Advantages /	A solution can be prepared from the tablets. Stability when stored in a glass bottle at 4° C can range from 7 to 56 days depending on syrup, distilled water, or distilled water with sodium ascorbate. Can be stored at 22° C for 14 days with distilled water and sodium ascorbate.	Available in IV dosage form.	
Pipeline	See last page of Class Review		
Efficacy/ Summary	See last page of Class Review		

ACE Inhibitors			
Characteristic	**Univasc (Moexipril)**	**Mavik (Trandolapril)**	**Altace (Ramipril)**
Pharmacology	Angiotensin-Converting Enzyme (ACE) Inhibitors (ACEIs) are peptides appearing to act primarily by suppression of the renin-angiotensin-aldosterone system. Renin (synthesized in the kidneys) is released into the circulation where it acts on angiotensinogen to produce angiotensin I, a relatively inactive decapeptide, which is then converted by ACE to angiotensin II, a potent endogenous vasoconstrictor. Angiotensin II stimulates aldosterone secretion from the adrenal cortex, contributing to sodium and fluid retention. ACEIs block the conversion of angiotensin I to angiotensin II by inhibiting ACE; they do not alter pressor responses to other agents. ACEIs may also inhibit local angiotensin II production at vascular and renal sites and attenuate the release of catecholamines from adrenergic nerve endings.		
Manufacturer		Abbott	Monarch; comarketed by King and Wyeth
Date of FDA Approval	Available generically	April 26, 1996	JAN 28, 1991 Patent expires JAN 27,2005 (pending other patents and litigation)
Generic available?	Yes	No	No
Dosage forms / route of admin.	Univasc/Moexipril Tablets: 7.5, 15 mg	Mavik Tablets: 1, 2, 4 mg	Altace Capsules: 1.25, 2.5, 5, 10 mg
	WITH HCTZ: Moexipril/HCTZ Uniretic 7.5/12.5, 15/12.5, 15/25 (not available generically)	**WITH VERAPAMIL:** trandolapril/verapamil: Tarka: 1/240, 2/180, 2/240, 4/240 mg tabs	
Dosing Frequency	QD or BID	QD or BID	QD or BID

ACE Inhibitors			
Characteristic	**Univasc (Moexipril)**	**Mavik (Trandolapril)**	**Altace (Ramipril)**

ACE Inhibitors

Characteristic	Univasc (Moexipril)	Mavik (Trandolapril)	Altace (Ramipril)
General Dosing Guidelines	**Hypertension** ▪ Initial: 7.5 mg 1 hour prior to meals QD. ▪ Maintenance: 7.5 to 30 mg daily in QD or BID 1 hour before meals. Total daily dosages > 60 mg/day have not been studied. **Renal function impairment:** Cautiously begin with 3.75 mg QD in patients with Ccr of = 40 ml/min; maximum of 15 mg/day.	**Hypertension** ▪ Initial: 1 mg/day (2 mg/day in black patients). Little experience with doses > 8 mg. Dosage adjustments can be made after at least 1 week. ▪ Maintenance: Inadequate control at 4 mg QD can be increased to 4 mg BID. **Heart failure post-MI or left-ventricular dysfunction post-MI:** ▪ Initial: 1 mg/day. Titrate, as tolerated, up to a target dose of 4 mg/day. **Renal/hepatic function impairment** ▪ Initial: 0.5 mg/day if Ccr < 30 mL/min or hepatic cirrhosis.	**Reduction in risk of MI, stroke, and death from cardiovascular causes:** In patients 55 years of age at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by 1 other cardiovascular risk factor (eg, hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, documented microalbuminuria), to reduce the risk of MI, stroke, or death from cardiovascular causes. Initial: 2.5 mg QD for 1 week, 5 mg QD for the next 3 weeks, and then increased as tolerated to maintenance dose. ▪ Maintenance: 10 mg QD. Can be given divided. ▪ Renal function impairment: Ccr of < 40 mL/min doses only 25% of those normally used should be given. **Hypertension** ▪ Initial: 2.5 mg QD. ▪ Maintenance dosage: 2.5-20 mg/day as QD or in 2 equally divided doses. ▪ Renal function impairment: Ccr of < 40 mL/min use 1.25 mg QD; maximum of 5 mg/day. **Heart failure post-MI** ▪ Initial: 2.5 mg BID. (1.25 mg BID if patient becomes hypotensive). ▪ Target dose of 5 mg BID. Titrate about every 3 weeks. ▪ Renal function impairment: Ccr of < 40 mL/min use 1.25 mg QD; maximum dose of 2.5 mg BID.

ACE Inhibitors			
Characteristic	**Univasc (Moexipril)**	**Mavik (Trandolapril)**	**Altace (Ramipril)**
Pediatric Labeling	▪ Safety and efficacy have not been established.		
FDA Labeled Indications	▪ Hypertension	▪ Hypertension ▪ CHF post-AMI ▪ LVD post-AMI	▪ Hypertension ▪ CHF post-AMI ▪ Reduction in Risk of MI, Stroke, & Death from CV Causes in high risk patients (as defined in dosing guidelines)
Other studied uses	N/a	▪ Reduces mortality in LVD post MI (TRACE)	▪ Reduces progression of hypertensive renal disease in black men more than (Norvasc) amlodipine (AASK)
Contraindications	Angioedema: ACE inhibitor-induced, history of, hereditary or idiopathic. Hypersensitivity to any ACE inhibitor, pregnancy Renal artery stenosis (solitary kidney or bilateral disease)		
Drug interactions	NSAIDs, Probenecid (captopril), Rifampin (enalapril), Allopurinol (captopril), Lithium, Potassium preparations/Potassium-sparing diuretics, Tetracycline (quinapril).		
Major Aes / Warnings	▪ First dose syncope, cough, angioedema sinusitis, headache, pharyngitis, vomiting, ALT increase, male sexual dysfunction ▪ Pregnancy: Category C (first trimester); Category D (second and third trimester). When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme inhibitors (ACEI's) can cause injury to and even death in the developing fetus. When pregnancy is detected, discontinue the ACE inhibitor as soon as possible. ▪ Lactation: Exercise caution. Consider the importance of the drug to the mother as to whether or not to discontinue nursing. ▪ Neutropenia/agranulocytosis, anaphylactic and related reactions, proteinuria, hypotension, renal function impairment, hepatic function impairment, hyperkalemia, cough		
Pharmacokinetics issues	▪ Protein binding: about 50% ▪ Affect of food on absorption: markedly reduced ▪ Prodrug: Moexiprilat	▪ Protein binding: about 80% ▪ Affect of food on absorption: reduced ▪ Prodrug: trandolaprilat	▪ Protein binding: about 73% for parent drug; about 56% for active metabolite ▪ Affect of food on absorption: slightly reduced ▪ Prodrug: ramiprilat
Dosage adjustment in key populations	▪ Dosage reduction or discontinuation may be required in those with renal impairment. ▪ Patients with hepatic impairment may require dosage adjustments of ramipril. ▪ Reduce dose of trandolapril for patients with a Ccr < 30 ml/min or with hepatic cirrhosis. ▪ Elderly patients may have higher blood levels and AUC of ramiprilat (active metabolite of ramipril) and moexiprilat (active metabolite of moexipril). However, decreased renal function may be more relevant than age.		
Unique Features / Advantages	N/a	N/a	Capsules can be opened and mixed with applesauce, apple juice or water. Storage of prepared mixtures: room temperature up to 24 hrs; under refrigeration up to 48 hrs.
Pipeline	See last page of Class Review		

ACE Inhibitors			
Characteristic	**Univasc (Moexipril)**	**Mavik (Trandolapril)**	**Altace (Ramipril)**
Efficacy/ Summary	See last page of Class Review		

ACE Inhibitors	
Characteristic	**Aceon (Perindopril)**
Pharmacology	Angiotensin-Converting Enzyme (ACE) Inhibitors (ACEIs) are peptides appearing to act primarily by suppression of the renin-angiotensin-aldosterone system. Renin (synthesized in the kidneys) is released into the circulation where it acts on angiotensinogen to produce angiotensin I, a relatively inactive decapeptide, which is then converted by ACE to angiotensin II, a potent endogenous vasoconstrictor. Angiotensin II stimulates aldosterone secretion from the adrenal cortex, contributing to sodium and fluid retention. ACEIs block the conversion of angiotensin I to angiotensin II by inhibiting ACE; they do not alter pressor responses to other agents. ACEIs may also inhibit local angiotensin II production at vascular and renal sites and attenuate the release of catecholamines from adrenergic nerve endings.
Manufacturer	Solvay
Date of FDA Approval	December 1993
Generic available?	No
Dosage forms / route of admin.	Aceon Tablets: 2 mg, 4 mg, 8 mg Oral
Dosing Frequency	QD or BID
General Dosing Guidelines	Uncomplicated hypertensive patients ▪ Initial: 4 mg QD. The dosage may be titrated upward to a maximum of 16 mg/day. ▪ Usual: 4-8 mg QD. It also may be administered in BID. BID dosing is only slightly superior. Use in elderly patients ▪ Initial dosages for the elderly (> 65 y) is 4 mg daily QD or divided BID to a max of 8 mg daily. Renal function impairment ▪ Ccr < 30 ml/min, safety and efficacy have not been established. Marked accumulation of active metabolite. ▪ Ccr > 30 ml/min, the initial dosage should be 2 mg/day titrated to a maximum of 8 mg/day. ▪ During dialysis, perindopril is removed with the same clearance as in patients with normal renal function; give dose within 4 hours after dialysis
Pediatric Labeling	Safety and efficacy have not been established.
FDA Labeled Indications	Hypertension
Other studied uses	▪ Clinical benefit in preventing recurrent stroke in hypertensive and normotensive patients (PROGRESS trial) ▪ Nephropathy prevention of progression in diabetic and non-diabetic patients ▪ CHF (PEP-HF Trial)

ACE Inhibitors	
Characteristic	**Aceon (Perindopril)**
Contraindications	Angioedema: ACE inhibitor-induced, history of, hereditary or idiopathic. Hypersensitivity to any ACE inhibitor, pregnancy Renal artery stenosis (solitary kidney or bilateral disease)
Drug interactions	NSAIDs, Probenecid (captopril), Rifampin (enalapril), Allopurinol (captopril), Lithium, Potassium preparations/Potassium-sparing diuretics, Tetracycline (quinapril).
Major AEs / Warnings	▪ First dose syncope, cough, angioedema, sinusitis, headache, pharyngitis, vomiting, ALT increase, male sexual dysfunction, ▪ Pregnancy: Category C (first trimester); Category D (second and third trimester). When used in pregnancy during the second and third trimesters, angiotensin-converting enzyme inhibitors (ACEI's) can cause injury to and even death in the developing fetus. When pregnancy is detected, discontinue the ACE inhibitor as soon as possible. ▪ Lactation: Exercise caution. Consider the importance of the drug to the mother as to whether or not to discontinue nursing. ▪ Neutropenia/ agranulocytosis, anaphylactic and related reactions, proteinuria, hypotension, renal fxn. Impairment, hepatic fxn. Impairment, hyperkalemia, cough
Pharmacokinetics issues	▪ Protein binding: 60% ▪ Affect of food on absorption: administer with or without food ▪ Prodrug: yes
Dosage adjustment in key populations	▪ Dosage reduction or discontinuation may be required in those with renal impairment. ▪ Starting dosage is same for elderly. Limited experience with doses > 8 mg in the elderly. ▪ Dialysis patients: dose after HD

ACEI SUMMARY	
Pipeline	Future products in this area mainly involve development of agents that alter the renin-angiotensin-aldosterone axis in order to decrease cardiovascular outcomes ▪ BK B2 receptor agonists: The nonapeptide bradykinin (BK) stimulates BK B(2) receptors. In various animal models and in humans it has been shown that the stimulation of BK B(2) receptors is not only implicated in the pathogenesis of inflammation, pain and tissue injury but also in powerful cardioprotective mechanisms. None of the currently known agonists of BK B(2) receptors--RMP-7 (lobradamil, Cereport; Alkermes), JMV-1116 (Fournier), FR-190997 (Fujisawa) and FR-191413 (Fujisawa)--have been selected for a clinical assessment in cardiovascular indications, but may once the it is known if there is a safe therapeutic window between potential cardioprotective and pro-inflammatory effects following BK B(2) receptor agonism. ▪ Endothelin receptor antagonists: Tracleer® (bosentan) marketed for pulmonary hypertension ▪ Vasopressin receptor antagonists: Vasopressin appears to adversely effect hemodynamics and cardiac remodeling, while potentiating the effects of norepinephrine and angiotensin II. The selective V(2) and dual V(1a)/V(2) receptor antagonists tolvaptan and conivaptan (Yamanouchi) respectively, substantially increase free water excretion and plasma osmolality, reduce body weight, improve symptoms of congestion, and moderately increase serum sodium concentrations in patients with heart failure who present with symptoms of fluid overload. ▪ Dual ACE/NEP inhibitor drugs (Vasopeptidase inhibitors): Drugs that possess the ability to inhibit simultaneously the membrane-bound zinc metalloproteases, angiotensin-converting enzyme (ACE), and the neutral endopeptidase EC 3.4.24.11 (NEP). 1. Omapatrilat (BMS), the most studied dual ACE/NEPinhibitor, had its initial NDA to the US FDA withdrawn by the MFT due to the high incidence of angioedema seen in ACE/NEP inhibitors over traditional ACEIs. At that time, BMS initiated large-scale trials to address this issue (OCTAVE, OPERA and OVERTURE). Thus far, OCTAVE has confirmed the antihypertensive efficacy of omapatrilat, but the rate of angioedema was three-fold higher than that normally seen with ACEIs. In OVERTURE, the rate of angioedema was comparable to that of enalapril, but omapatrilat was not superior to enalapril as antihypertensive therapy. 2. Samapatrilat: is another dual ACE/NEP inhibitor that is in Phase II clinical trials The future of this class of drugs will depend upon the tolerability of their side-effect profile and if high risk patients (patients at risk for angioedema) can be identified and excluded.

ACEI SUMMARY	
Summary / Efficacy	▪ American Diabetes Association Position Statement on diabetic nephropathy from January 2002 stated that in hypertensive patients with type 2 diabetes with microalbuminuria or clinical albuminuria, ARBs are the initial agents of choice. In hypertensive and nonhypertensive type 1 diabetic patients with microalbuminuria or clinical albuminuria, ACEIs are the initial agents of choice. The ADA states that if one class is not tolerated, the other class should be substituted. Specific agents were not chosen by the ADA. Capoten (Captopril) is the only ACEI with the indication for diabetic nephropathy; however, this is believed to be a class effect. ▪ ACEIs are recommended (unless there is a contraindication) as first line agents in patients with heart failure and in patients who have had myocardial infarction (with systolic dysfunction). ▪ In studies, ACEIs have been shown to have positive effects on the hemodynamics, clinical status and symptoms of CHF. There does not appear to be a statistical detectable heterogeneity of effect among ACEIs; the benefit in decreasing mortality rate was proposed to be a class effect. ▪ The following is from the American College of Cardiology/ American Heart Association (ACC/AHA) Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult. – Although most of the evidence supporting an effect of ACE inhibitors on the survival of patients with HF is derived from experience with enalapril, the available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival. – Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE inhibitors are superior to other ACE inhibitors in any clinical aspect of HF. – Nevertheless, in selecting among ACE inhibitors, it is recommended to give preference to ACE inhibitors that have been shown to reduce morbidity and mortality in clinical trials (captopril, enalapril, lisinopril, and ramipril), because these studies have clearly defined a dose that is effective in modifying the history of the disease. ▪ Attempts should be made to utilize ACE inhibitors at the doses shown to reduce the risk of cardiovascular events in clinical trials, and if these target doses cannot be used or are poorly tolerated, lower doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses (ATLAS trial).

ACEI SUMMARY	
Summary / Efficacy	▪ The HOPE trial gave Altace (Ramipril) the unique indication of : Reduction in risk of MI, stroke, and death from cardiovascular causes: In patients 55 years of age at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by 1 other cardiovascular risk factor (eg, hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, documented microalbuminuria), to reduce the risk of MI, stroke, or death from cardiovascular causes. (Trial editorial included in abstract section). It has been hypothesized (but not proven) that the high tissue-ACE binding affinity of Altace® may be responsible for the positive outcomes seen. For that reason, a discussion of tissue-ACE binding follows. ▪ Tissue ACE binding: Angiotensin converting enzyme (ACE) is found in various tissues, organs, endothelium and within the parenchyma of inflammatory cells. Activation of tissue ACE, causes endothelial dysfunction which may lead disruptions in the cardiovascular and renal system, thus leading to negative clinical outcomes. Different ACEI have different binding affinities for tissue ACEI, which has been hypothesized, but not proven, as being the rationale for differences among ACEI and their impact on clinical events (HOPE trial). The rank order of ACEI and their binding to tissue ACEI potency is as follows: Accupril (Quinapril)=Lotensin (Benazepril) > Altace (Ramipril) > Aceon (Perindropril) > Prinivil/Zestril (Lisinopril) > Vasotec (enalapril) > Monopril (Fosinopril) > Capoten (Captopril) ▪ IMAGINE, PEACE and EUROPA using Accupril (quinapril), Mavik (trandolapril) and Aceon (perindropril) respectively are trials using high tissue ACE binding ACEI in trials that are very similar (but not identical to that of the HOPE study (Altace)). Once concluded, and if positive, these studies may confirm the findings of the HOPE study and validate the use of tissue-ACE inhibitors in high risk patients. ▪ Vasotec (Enalapril), Monopril (Fosinopril), Altace (ramipril), Mavik (trandolapril) have an average trough-peak ration greater than 50% from data from published studies, thus fulfilling the FDA recommendation that once daily formulations have a trough-peak ratio of greater than 50%. According to FDA labeling, all ACEI may be dosed once daily with the exception of captopril.

Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM.

Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F.

Diabetes Care. 1998 Apr;21(4):597-603.
Centro Diabetico Ospedale di Marino, Italy.

OBJECTIVE: ACE inhibitors and calcium antagonists may favorably affect serum lipids and glucose metabolism. The primary aim of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) was to compare the effects of fosinopril and amlodipine on serum lipids and diabetes control in NIDDM patients with hypertension. Prospectively defined cardiovascular events were assessed as secondary outcomes. RESEARCH DESIGN AND METHODS: Inclusion criteria included a diagnosis of NIDDM and hypertension (systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg). Exclusion criteria included a history of coronary heart disease or stroke, serum creatinine > 1.5 mg/dl, albuminuria > 40 micrograms/min, and use of lipid-lowering drugs, aspirin, or antihypertensive agents other than beta-blockers or diuretics. A total of 380 hypertensive diabetics were randomly assigned to open-label fosinopril (20 mg/day) or amlodipine (10 mg/day) and followed for up to 3.5 years. If blood pressure was not controlled, the other study drug was added. RESULTS: Both treatments were effective in lowering blood pressure. At the end of follow-up, between the two groups there was no significant difference in total serum cholesterol, HDL cholesterol, HbA1c, fasting serum glucose, or plasma insulin. The patients receiving fosinopril had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina than those receiving amlodipine (14/189 vs. 27/191; hazards ratio = 0.49, 95% CI = 0.26-0.95). CONCLUSIONS: Fosinopril and amlodipine had similar effects on biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major vascular events, compared with the patients randomized to amlodipine.

Angiotensin-converting enzyme inhibitors and kidney protection: the AIPRI trial. The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group.

Maschio G, Alberti D, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Janin G, Zucchelli P.

J Cardiovasc Pharmacol. 1999;33 Suppl 1:S16-20; discussion S41-3.

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A protective effect of angiotensin-converting enzyme (ACE) inhibitors has been shown in patients with diabetic nephropathy but has not been clearly established in nondiabetic renal disease. A multicenter European study was designed to determine whether the ACE inhibitor benazepril was safe and effective in protecting residual renal function in patients with various renal diseases and mild to moderate renal failure. The trial involved 583 patients from 49 centers in Italy, France, and Germany. The patients were randomized to receive benazepril or placebo plus other antihypertensive agents, the target being a diastolic blood pressure of less than 90 mm Hg. Thirty-one patients in the benazepril group and 57 patients in the placebo group reached the end point [the time elapsed from entry to (a) doubling of serum creatinine (SCr) concentrations and (b) start of renal replacement therapy; $p < 0.001$ at 3 years]. The associated reduction in the relative risk of reaching the end point was 53% in benazepril-treated patients, with actuarial renal survival probability significantly better at 3 years. The best survival of renal function was observed in patients with chronic glomerular diseases and proteinuria greater than 1.0 g/24 h. Benazepril is effective in slowing the rate of progression and improving the survival of renal function in patients with renal diseases of various origins. This protective effect is associated with a clinically relevant decrease in both blood pressure and proteinuria.

Pathophysiologic and therapeutic importance of tissue ACE: a consensus report.

Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlof B, Deanfield J, Diez J, Drexler H, Ferrari R, Van Gilst W, Hansson L, Hornig B, Husain A, Johnston C, Lazar H, Lonn E, Luscher T, Mancini J, Mimran A, Pepine C, Rabelink T, Remme W, Ruilope L, Ruzicka M, Schunkert H, Swedberg K, Unger T, Vaughan D, Weber M.

Cardiovasc Drugs Ther. 2002 Mar;16(2):149-60.
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Angiotensin-converting enzyme (ACE) activation and the de novo production of angiotensin II contribute to cardiovascular disease through direct pathological tissue effects, including vascular remodeling and inflammation, as well as indirect action on nitric oxide bioavailability and its consequences. The endothelium plays a pivotal role in both vascular function and structure; thus, the predominant localization of ACE to the endothelium has implications for the pathobiology of vascular disease, such as coronary artery disease. Numerous experimental studies and clinical trials support the emerging realization that tissue ACE is a vital therapeutic target, and that its inhibition may restore endothelial function or prevent endothelial dysfunction. These effects exceed those attributable to blood pressure reduction alone; hence, ACE inhibitors may exert an important part of their effects through direct tissue action. Pharmacologic studies show that while ACE inhibitors may differ according to their binding affinity for tissue ACE the clinical significance remains to be determined.

Perindopril alters vascular angiotensin-converting enzyme, AT(1) receptor, and nitric oxide synthase expression in patients with coronary heart disease.

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Hypertension. 2002 Feb;39(2 Pt 2):634-8.
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Angiotensin-converting enzyme inhibitors (ACEi) reduce cardiovascular morbidity and mortality by improving coronary perfusion, reducing ventricular hypertrophy and remodeling, and preventing progression of coronary atherosclerosis. However, the cellular mechanisms underlying the beneficial effects of ACEi are not fully understood. We studied the in vivo effects of ACE inhibition with perindopril on cellular expression of ACE, AT(1) receptors and 2 nitric oxide synthase (NOS) isoforms, endothelial (eNOS) and inducible NOS (iNOS), in human blood vessels using quantitative in vitro autoradiography and immunocytochemistry. Seven patients with ischemic heart disease were treated with perindopril (4 mg/d) for up to 5 weeks before elective coronary bypass surgery, whereas controls did not receive the ACEi (n=7). Perindopril decreased plasma ACE by 70% and the plasma angiotensin II to angiotensin I ratio by 57% and reduced vascular ACE to approximately 65% of control levels in both endothelium and adventitia. By contrast, AT(1) receptor binding in vascular smooth muscle cells was increased by 80% in patients treated with perindopril as confirmed by immunocytochemistry. eNOS was expressed primarily in endothelial cells, whereas little iNOS expression occurred in vascular smooth muscle cells of untreated patients. Both eNOS and iNOS expression seemed to increase during perindopril treatment. These results suggest that suppression of angiotensin II formation in the vascular wall and increased expression of eNOS and iNOS during ACE inhibition may be beneficial in reversing endothelial dysfunction in patients with cardiovascular disease. Because vascular AT(1) receptor expression is increased during chronic ACE inhibition, more clinical studies are required to determine whether it is necessary to combine ACE inhibitors and AT(1) receptor antagonists in clinical management of heart failure, coronary heart disease, and hypertension

The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data.

Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlof B, Deanfield J, Diez J, Drexler H, Ferrari R, van Gilst W, Hansson L, Hornig B, Husain A, Johnston C, Lazar H, Lonn E, Luscher T, Mancini J, Mimran A, Pepine C, Rabelink T, Remme W, Ruilope L, Ruzicka M, Schunkert H, Swedberg K, Unger T, Vaughan D, Weber M; Working Group on Tissue Angiotensin-converting enzyme, International Society of Cardiovascular Pharmacotherapy.

Am J Cardiol. 2001 Nov 8;88(9 Suppl):1L-20L.
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Angiotensin-converting enzyme (ACE) is primarily localized (>90%) in various tissues and organs, most notably on the endothelium but also within parenchyma and inflammatory cells. Tissue ACE is now recognized as a key factor in cardiovascular and renal diseases. Endothelial dysfunction, in response to a number of risk factors or injury such as hypertension, diabetes mellitus, hypercholesteremia, and cigarette smoking, disrupts the balance of vasodilation and vasoconstriction, vascular smooth muscle cell growth, the inflammatory and oxidative state of the vessel wall, and is associated with activation of tissue ACE. Pathologic activation of local ACE can have deleterious effects on the heart, vasculature, and the kidneys. The imbalance resulting from increased local formation of angiotensin II and increased bradykinin degradation favors cardiovascular disease. Indeed, ACE inhibitors effectively reduce high blood pressure and exert cardio- and renoprotective actions. Recent evidence suggests that a principal target of ACE inhibitor action is at the tissue sites. Pharmacokinetic properties of various ACE inhibitors indicate that there are differences in their binding characteristics for tissue ACE. Clinical studies comparing the effects of antihypertensives (especially ACE inhibitors) on endothelial function suggest differences. More comparative experimental and clinical studies should address the significance of these drug differences and their impact on clinical events.

Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria

The EUCLID study group
The Lancet
Volume 349, Issue 9068 , 21 June 1997, Pages 1787-1792

Abstract

Background Renal disease in people with insulin-dependent diabetes (IDDM) continues to pose a major health threat. Inhibitors of angiotensin-converting enzyme (ACE) slow the decline of renal function in advanced renal disease, but their effects at earlier stages are unclear, and the degree of albuminuria at which treatment should start is not known.

Methods We carried out a randomised, double-blind, placebo-controlled trial of the ACE inhibitor lisinopril in 530 men and women with IDDM aged 20–59 years with normoalbuminuria or microalbuminuria. Patients were recruited from 18 European centres, and were not on medication for hypertension. Resting blood pressure at entry was at least 75 and no more than 90 mm Hg diastolic, and no more than 155 mm Hg systolic. Urinary albumin excretion rate (AER) was centrally assessed by means of two overnight urine collections at baseline, 6, 12, 18, and 24 months.

Findings There were no differences in baseline characteristics by treatment group; mean AER was 8·0 g/min in both groups; and prevalence of microalbuminuria was 13% and 17% in the placebo and lisinopril groups, respectively. On intention-to-treat analysis at 2 years, AER was 2·2 g/min lower in the lisinopril than in the placebo group, a percentage difference of 18·8% (95% CI 2·0–32·7, p=0·03), adjusted for baseline AER and centre, absolute difference 2·2 g/min. In people with normoalbuminuria, the treatment difference was 1·0 g/min (12·7% [-2·9 to 26·0], p=0·1). In those with microalbuminuria, however, the treatment difference was 34·2 g/min (49·7% [-14·5 to 77·9], p=0·1; for interaction, p=0·04). For patients who completed 24 months on the trial, the final treatment difference in AER was 38·5 g/min in those with microalbuminuria at baseline (p=0·001), and 0·23 g/min in those with normoalbuminuria at baseline (p=0·6). There was no treatment difference in hypoglycaemic events or in metabolic control as assessed by glycated haemoglobin.

Interpretation Lisinopril slows the progression of renal disease in normotensive IDDM patients with little or no albuminuria, though greatest effect was in those with microalbuminuria (AER20 g/min). Our results show that lisinopril does not increase the risk of hypoglycaemic events in IDDM.

Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack

Lancet

Volume 358, Issue 9287 , 29 September 2001, Pages 1033-1041

PROGRESS Collaborative Group,

Abstract

Background Blood pressure is a determinant of the risk of stroke among both hypertensive and non-hypertensive individuals with cerebrovascular disease. However, there is uncertainty about the efficacy and safety of blood-pressure-lowering treatments for many such patients. The perindopril protection against recurrent stroke study (PROGRESS) was designed to determine the effects of a blood-pressure-lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack.

Methods 6105 individuals from 172 centres in Asia, Australasia, and Europe were randomly assigned active treatment (n=3051) or placebo (n=3054). Active treatment comprised a flexible regimen based on the angiotensin- converting-enzyme inhibitor perindopril (4 mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. The primary outcome was total stroke (fatal or non-fatal). Analysis was by intention to treat.

Findings Over 4 years of follow up, active treatment reduced blood pressure by 9/4 mm Hg. 307 (10%) individuals assigned active treatment suffered a stroke, compared with 420 (14%) assigned placebo (relative risk reduction 28% [95% CI 17–38], p<0·0001). Active treatment also reduced the risk of total major vascular events (26% [16–34]). There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (all p<0·01). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43% (30–54). Single-drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.

Interpretation This blood-pressure-lowering regimen reduced the risk of stroke among both hypertensive and non-hypertensive individuals with a history of stroke or transient ischaemic attack. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions than did single drug therapy with perindopril alone. Treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischaemic attack, irrespective of their blood pressure.

Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study.

Dagenais GR, Yusuf S, Bourassa MG, Yi Q, Bosch J, Lonn EM, Kouz S, Grover J; HOPE Investigators.
Circulation. 2001 Jul 31;104(5):522-6.

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BACKGROUND: In trials of patients with left ventricular dysfunction or heart failure, ACE inhibitor use was unexpectedly associated with reduced myocardial infarction (MI). Using the Heart Outcomes Prevention Evaluation (HOPE) trial data, we tested prospectively whether ramipril, an ACE inhibitor, could reduce coronary events and revascularization procedures among patients with normal left ventricular function. METHODS AND RESULTS: In the HOPE trial, 9297 high-risk men and women, >/=55 years of age with previous cardiovascular disease or diabetes plus 1 risk factor, were randomly assigned to ramipril (up to 10 mg/d), vitamin E (400 IU/d), their combination, or matching placebos. During the mean follow-up of 4.5 years, there were 482 (10.4%) patients with clinical MI and unexpected cardiovascular death in the ramipril group compared with 604 (12.9%) in the placebo group [relative risk reduction (RRR), 21% (95% CI) (11,30); P<0.0003]. Ramipril was associated with a trend toward less fatal MI and unexpected death [4.0% versus 4.7%; RRR, 16% (-3, 31)] and with a significant reduction in nonfatal MI [5.6% versus 7.2%; RRR, 23% (9,34)]. Risk reductions in MI were documented in participants taking or not taking beta-blockers, lipid lowering, and/or antiplatelet agents. Although ramipril had no impact on hospitalizations for unstable angina [11.9% versus 12.2%; RRR, 3% (-9,14)], it reduced the risk of worsening and new angina [27.2% versus 30.0%; RRR, 12% (5,18); P<0.0014] and coronary revascularizations [12.5% versus 14.8%; RRR, 18%; (8,26) P<0.0005]. CONCLUSIONS: In this high-risk cohort, ramipril reduced the risk of MI, worsening and new angina, and the occurrence of coronary revascularizations.

The Heart Outcomes Prevention Evaluation study: angiotensin-converting enzyme inhibitors: are their benefits a class effect or do individual agents differ?
Editorial Review
Current Opinion in Nephrology and Hypertension 2001, 10:597-601

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Abstract

The Heart Outcomes Prevention Evaluation study was a landmark study employing the angiotensin-converting enzyme inhibitor ramipril in a patient population pre-destined for vascular events. This study found that a 10 mg dose of ramipril in comparison with placebo reduced the incidence of death, myocardial infarction, stroke, and death from cardiovascular causes by 22%. This improvement in outcome was viewed as a direct consequence of ramipril, although the fact that blood pressure was reduced with ramipril has cast some considerable doubt on this supposition. Whether the observed findings in this study are a 'class effect' for all angiotensin-converting enzyme inhibitors is unclear. To its credit, ramipril is the first angiotensin-converting enzyme inhibitor shown to prevent ischemic events in high-risk patients without discernible left ventricular dysfunction. Other similar trials are underway, which are studying similar populations to those included in this landmark study and should resolve the question of whether the cardioprotective effects of angiotensin-converting enzyme inhibitors are a 'class effect'.

Introduction

The concept of inhibiting the renin-angiotensin system (RAS) to treat hypertension was first conceived in the early 1980s and was formally tested as angiotensin-converting enzyme (ACE) inhibitors became available. Shortly thereafter, the importance of RAS inhibition was extended to the management of congestive heart failure (CHF) and subsequently consolidated with several landmark studies including the Studies of Left Ventricular Dysfunction (SOLVD) [1,2] and the Vasodilator Heart Failure Trial II [3]. Other studies in the post-myocardial infarction population, including the Survival and Ventricular Enlargement (SAVE) trial [4], the Acute Infarction Ramipril Efficacy (AIRE) study [5], and the Trandolapril Cardiac Evaluation study [6], revealed an important role for ACE inhibitors in decreasing morbidity and mortality in this at high-risk population. Over the last decade, considerable evidence has been amassed in support of the concept that an activated RAS is an important risk factor for vascular disease, independent of other cardiovascular risk factors. These studies, both experimental and clinical, supported the intriguing possibility that patients at risk for end events could benefit from inhibition of the RAS system with ACE inhibitor therapy.

Trial design

The Heart Outcomes Prevention Evaluation (HOPE) study was a large simple, factorial design, double-blind, placebo-controlled trial, which determined the risk of cardiovascular events in over 9500 patients [7]. The patients were studied in 267 centers in 19 countries. These patients were considered at high risk for future vascular death or morbidity by way of age, in that they were required to be older than 55 years or because they had either diabetes or evidence of a prior vascular event or existing vascular disease. Patients also could not have CHF or an ejection fraction known to be below 40%. Those with diabetes were required to have either a known vascular disease or one other risk factor for cardiovascular disease, such as cigarette smoking, a blood pressure >140/90 mmHg or elevated cholesterol (>5.2 mmol/l). Patients with diabetes were included in this study because even without recognizable coronary artery disease they have an equivalent risk for coronary events as nondiabetic patients with established coronary disease [8].

Patients already receiving vitamin E or for whom an ACE inhibitor was indicated, such as those with left ventricular dysfunction, were specifically excluded from the study. The HOPE protocol included a run-in period for tolerance. During this period, all 10 576 initially eligible patients received a 2.5 mg dose of ramipril for 7-10 days, thereafter they received a matching placebo for 10-14 days. This approach hoped to identify those prone to early side effects and those who experienced an exclusionary change in serum electrolytes or creatinine. Approximately 10% of the population or 1035 patients were excluded for these reasons. The remaining 9541 subjects were randomized to ramipril or placebo, beginning with a titration phase of 2.5 mg/day for 1 week, followed by 5 mg/day for 3 weeks, and thereafter patients received 10 mg/day until study completion. Follow-up was at 1 month and thereafter semi-annually. All patients received either vitamin E (400 IU) or matching placebo [9]. A sub-study including 244 patients compared a low dose of ramipril (2.5 mg/day) with a full dose (10 mg/day) or with placebo. The results of this sub-study are yet to be reported.

Population at risk and study aims

The aims of the HOPE study were to answer two questions. First, would an ACE inhibitor reduce the risk for coronary heart disease events, death, and stroke in high-risk patients without heart failure? Second, does vitamin E reduce the risk for these same events? Experimental and clinical evidence existed in support of both of these hypotheses, thereby justifying their study. Ramipril, the ACE inhibitor employed in this study, was originally approved in 1991 for the treatment of hypertension and has since gained an indication for reducing the risk of death and heart failure among patients having experienced a myocardial infarction. Of the patients in the HOPE study, 27% were women, 55% were at least 65 years of age, 88% had cardiovascular disease, 47% had hypertension, and 38% had diabetes.

The study was unusual in that the trial interventions were added, in the majority of patients, to other proven medications, which would be expected to reduce the impact of the trial regimen. At baseline, 76% of the subjects were on an antiplatelet agent (mostly aspirin), 45% on a calcium-channel blocker, 40% on a [beta]-blocker, 15% on a diuretic and 30% on a lipid-lowering agent. During the 4.5 years of the study the use of all of these agents went up with the exception of calcium-channel blockers, which decreased in use by 5%. Perhaps as a result of these background therapies, the baseline blood pressure was normal at 139/79 mmHg in the overall population. This was despite a history of hypertension in almost 50% of the study population.

The reduction in blood pressure attributable to ramipril was modest - a difference of about 3-4 mmHg systolic and 1-2 mmHg diastolic between ramipril and placebo allocated patients. The HOPE study, however, did not set out to be a hypertension trial and the frequency with which blood pressure readings were obtained makes it difficult to interpret the observed differences in blood pressure. The ramipril treatment arm of this study differed from other studies in three ways. First, the baseline blood pressure was at or near normal in the study participants; second, the treatment-induced reduction in blood pressure was very modest; and finally, there was extensive use of concomitant anti-hypertensive, anti-platelet, and lipid-lowering therapies, although these were equally distributed in the ramipril and placebo treatment groups.

Results

The HOPE study showed that ramipril was well tolerated, with the large majority of patients continuing on the full 10 mg dose. There was only a 7.3% excess drop out rate because of ramipril-related cough. In the ramipril group 82.9% of patients were still taking medication at 1 year, 74.7% at 2 years, 70.9% at 3 years, and 62.5% at 4 years. The actual numbers of patients taking any ACE inhibitor (including ramipril) were actually higher, with 87.4% of patients in the ramipril group taking either ramipril or an open-label ACE inhibitor at 1 year and 75.2% of the patients taking an ACE inhibitor at 4 years. In the placebo group, 10.8% of the patients were receiving an open-label ACE inhibitor at year 4.

The primary endpoint was defined as a combination of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The trial was stopped about 1 year early, after 4.5 years of treatment, on the advice of the Data and Safety Monitoring Committee, since the weight of the available evidence strongly supported a more favorable outcome in the ramipril-treated group. During the study period 17.8% of subjects in the placebo group reached the primary combined endpoint compared with 14% in the ramipril-treated group. This difference represented a 22% reduction in relative risk. The individual components of the composite endpoint were also significantly reduced by 32% for stroke, 26% for cardiovascular death, and 20% for myocardial infarction. Ramipril also reduced the risk of several other clinical endpoints, including CHF by 23% and revascularization procedures by 15%. All cause mortality was reduced by 16% with the Kaplan-Meier survival curves diverging by 1 year with continued separation of these curves until the trial was terminated [7].

Non-cardiovascular mortality was equal in the ramipril and placebo treatment groups. A noteworthy feature of the results was the consistency of the findings over a wide range of prespecified sub-group analyses. The results were also the same irrespective of concomitant baseline antihypertensive medications and whether or not patients were taking [beta]-blockers, calcium-channel blockers, diuretics, or lipid-lowering agents. In addition, in patients with pre-existing vascular disease or diabetes combined with an additional cardiovascular risk factor, mild renal insufficiency (serum creatinine of 1.4 mg/dl or greater), the risk for subsequent cardiovascular events was significantly increased. Ramipril reduced cardiovascular risk without increasing adverse effects independent of the level of renal function [10].

In contradistinction to the positive findings with ramipril, vitamin E had no discernible effects on any of the outcome variables [9]. The reasons why vitamin E treatment provided no additional benefit are unclear. It is speculated that the study may not have been of sufficient length to show a response to antioxidant therapy or that for vitamin E to show a positive effect, it must be given together with other antioxidant therapy such as vitamin C. An unexpected finding in the HOPE study was that ramipril-treated patients experienced a 33% reduction in the onset of new diabetes during the 4.5 years of the trial, which supports the similar, though less pronounced, reduction in new onset diabetes observed in the Captopril Prevention Project study [11]. Since this was not a pre-specified endpoint, this finding requires appropriate prospective studies before it can be accepted.

Evidence for a benefit beyond blood pressure reduction

The reduction in event rates, particularly for myocardial infarctions, was much greater than would be expected from such a modest fall in blood pressure as was observed in the ramipril treatment limb of this study. The oft quoted meta-analysis of blood pressure lowering trials using older agents would suggest a reduction in stroke of 38% and in myocardial infarction of only 16% when diastolic blood pressure is reduced by 4-5 mmHg over a period of 4-5 years [12]. The HOPE study achieved this reduction in event rates with a fraction of this diastolic blood pressure reduction. It has been argued that the high-risk populations in the HOPE study might, by reason of additional risk factors, have a steeper risk gradient for specific change in blood pressure values. The risk reduction in the ramipril group was, however, much greater than would have been inferred from the blood pressure/risk gradient seen in the placebo arm of the HOPE study. Further evidence to support a major non-blood pressure effect of ramipril is provided by a multiple regression analysis of the patients with diabetes in the HOPE study, which showed a relative reduction in risk even after allowing for the effect of the reduction in blood pressure [13].

When the benefits of ramipril were related to quartile of baseline blood pressure, greater risk reduction was shown in patients with higher baseline systolic blood pressure (unpublished data). This latter observation again points to the influential role of blood pressure reduction in the genesis of end-organ protection.

The MICRO-HOPE study

The results on the 3577 diabetic subjects in the HOPE study were even more striking than the findings of the main study [13]. These findings, however, are most applicable to patients with type II diabetes in that only 81 of the 3577 patients with diabetes in the HOPE study were type I diabetics. There was a highly significant risk reduction of 25% for the combined primary outcome, 22% for myocardial infarction, 33% for stroke and 37% for cardiovascular death. In addition, overt nephropathy was reduced by 24%. As was observed in the main study the benefits observed were consistent across literally all sub-groups and occurred independently of age and gender and regardless of whether patients were taking [beta]-blockers, aspirin, or lipid-lowering agents. The striking nature of these findings in the patients with diabetes are not surprising in light of the results from the UK Prospective Diabetes Study [14] and the Hypertension Optimal Treatment [15] study. Both of these studies showed a clear cardiovascular benefit to reducing blood pressure [16].

Mechanisms of benefit

The results of the HOPE study are highly suggestive of a specific vasculoprotective effect for ramipril above and beyond that anticipated from the modest blood pressure reduction observed in this study. The mechanism for such vasculoprotection can only be speculated on. Undoubtedly, some contribution to the positive outcome derived from a negation of cellular effects of angiotensin II. Such cellular effects of angiotensin II include intimal and vascular smooth muscle cell proliferation as well as plaque instability. The relatively rapid benefit afforded patients in the HOPE study suggest an important role for plaque stabilization [17]. This latter hypothesis is particularly appealing since recent studies with ramipril suggest that it has minimal effect on reducing atherosclerosis [18]. Furthermore, the Trial on Reversing Endothelial Dysfunction study previously showed that ACE inhibition with quinapril improved endothelial dysfunction in normotensive patients who were without evidence of severe hyperlipidemia or CHF [19]. Improvement of endothelial function is recognized as a means by which plaques can be stabilized.

Class effect

The experimental rationale of the HOPE study was solid. It was based on the recognized actions of angiotensin II and the countervailing actions of ACE inhibitors with conceptual support from meta-analysis of the SOLVD and SAVE trials [1,2,4,20]. Accordingly, the benefits of ramipril in the HOPE study might thus be viewed as a class effect for ACE inhibitors. Acceptance of the concept of a class effect, however, requires a denial of the fact that ACE inhibitors are structurally and physicochemically distinct [21]. ACE inhibitors have differing potency, pharmacokinetics, and lipophilicity. The concept of lipophilicity, although much debated, remains clinically ethereal. Few studies have been able to show reproducible differences in clinical effects amongst the ACE inhibitors based solely on the property of lipophilicity [22]. Furthermore, ACE inhibitor tissue penetration, of which lipophilicity is but one determinant, may be influenced by ACE inhibitor blood levels. Thus, ACE inhibitor pharmacokinetics is of some relevance to the duration and extent of tissue ACE inhibition.

As much as the concept of class effect for ACE inhibitors has been espoused, a true operational definition for ‘class effect’ does not exist for ACE inhibitors or for that matter any class of drugs. Instead a related term ‘class labeling’ is the terminology preferred by the Food and Drug Administration. Further confusing the issue is the inherent difficulty in identifying dose equivalence for the various positive effects of ACE inhibitors [22,23]. For example, true dose equivalence for blood pressure control has never been determined amongst the various ACE inhibitors. The impression that equivalent doses are readily identifiable in the hypertensive patient is merely an outgrowth of the unique dose-response relationships for ACE inhibitors. ACE inhibitors have a steep dose-response at low doses and thereafter when given in higher doses a relatively flat dose-response curve [24]. This dose-response pattern lends itself readily to the concept of class effect. The issue of class effect is more dubious when CHF is considered for treatment with ACE inhibitors. The dose amounts for ACE inhibitors in CHF and the typically altered pharmacokinetics of these drugs in the CHF patient make it highly doubtful that a dose could be identified to allow one ACE inhibitor to ever truly be interchangeable with another without formal testing [25-27].

Where then does the concept of class effect fall for tissue protection and, in particular, how does it relate to the HOPE study? Although at this time the answer to this question is still unclear it is possible that the physicochemical features of ramipril distinguish it from a tissue protection viewpoint. Yet, the original premise of the HOPE study was not to study a highly tissue-bound ACE inhibitor; rather, the intent was to study the ACE inhibitor ramipril compared to placebo. After the fact, the physicochemical features of this compound were marshaled as an explanation for the observed findings. If the original intent of this study was to compare a highly tissue-bound ACE inhibitor with an ACE inhibitor less tissue bound, then this should have been part of the experimental question. If the HOPE results are ultimately shown to be a derivative of the blood pressure change observed in this study then there is little to distinguish ramipril from the nine other ACE inhibitors currently marketed in the USA [26,27].

Implications of the HOPE study

These results show substantial benefits in mortality and morbidity from the use of ramipril in a large group of patients at high risk for future cardiovascular events [28,29]. The results of the HOPE study were of sufficient significance to prompt the American Heart Association to include this study in its top ten list of research advances for the year 1999. In addition, the Food and Drug Administration recently allowed the findings of the HOPE study to be incorporated into the package label for ramipril.

The results of the HOPE study were achieved over and above conventional treatment and therefore are broadly applicable to clinical practice. The implications for diabetic patients are particularly striking from this study. These results should extend the use of ACE inhibitors to a much wider group of patients. ACE inhibitor therapy has previously been shown to be of proven benefit to those with left ventricular dysfunction, hypertension, or diabetes with proteinuria. ACE inhibitor use can now be extended to a different patient group - those at risk for vascular events but without substantive evidence for left ventricular dysfunction, many of who are receiving aspirin prophylaxis. Finally, the HOPE study findings provide the factual underpinnings for conducting additional studies, employing differing pharmacologic approaches to interruption of the RAS in at-risk patients. Alternatively, the HOPE study was not designed to determine whether ACE inhibitors are the optimal agents for preventing cardiovascular events in high-risk hypertensive patients. This issue is being addressed in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack trial, in which patients with hypertension and at least one additional risk factor are currently randomized to an ACE inhibitor, a calcium-channel blocker, or a thiazide diuretic. This study will be completed in 2002.

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<table>
<tr><th colspan="4">Angiotensin II Receptor Blockers (ARBs)</th></tr>
<tr><th>Characteristic</th><th>Atacand
(Candesartan)</th><th>Avapro
(Irbesartan)</th><th>Cozaar
(Losartan)</th></tr>
<tr><td>Pharmacology</td><td colspan="3">Losartan, candesartan, irbesartan, telmisartan, olmesartan and valsartan are angiotensin II receptor (type AT1) antagonists. Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [ACE; kininase II]) is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin-aldosterone system (RAAS), and an important component in the pathophysiology of HTN. Its effects are vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Angiotensin II receptor antagonists (ARBs) block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor in many tissues (adrenal gland, heart, brain, fetus and injured tissues), but it is not known to be associated with cardiovascular homeostasis. A third receptor AT3 has been discovered in the neuroblastoma cells in amphibians, and a fourth, AT4 (found in brain, heart, lung, prostate, kidney, adrenal gland of humans and mice)is thought to be a renal vasodilator and is thought to stimulate plasminogen activator inhibitor 1. ARBs have a selective affinity for the AT1 receptor.

ARBs do not inhibit ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. ARBs do not affect the response to bradykinin, whereas ACE inhibitors do increase the response. In spite of the decreasing aldosterone secretion, ARBs have very little effect on serum potassium.</td></tr>
<tr><td>Generic available?</td><td>No</td><td>No</td><td>No</td></tr>
<tr><td>Manufacturer</td><td>Astra-Zenca</td><td>Bristol Meyers Squibb, Sanofi-Synthelabo</td><td>Merck</td></tr>
<tr><td>Date of FDA approval</td><td>June 4, 1998</td><td>September 30, 1997.</td><td>April 14, 1995.</td></tr>
<tr><td>Dosage forms / route of admin.</td><td>Atacand Tablets: 4 mg, 8 mg, 16 mg, 32 mg
With HCTZ☹candesartan/HCTZ)
Atacand HCT: 16/12.5, 32/12.5 mg</td><td>Avapro Tablets: 75 mg, 150 mg, 300 mg
With HCTZ: (irbesartan/HCTZ)
Avalide: 150/12.5, 300/12.5mg</td><td>Cozaar Tablets: 25 mg, 50 mg, 100 mg
With HCTZ: (losartan/HCTZ)
Hyzaar: 50/12.5, 100/25mg</td></tr>
</table>

Angiotensin II Receptor Blockers (ARBs)			
Characteristic	**Atacand (Candesartan)**	**Avapro (Irbesartan)**	**Cozaar (Losartan)**
Generalized dosing guidelines	▪ Administer with or without food. ▪ BP response is dose-related over the range of 2-32 mg. ▪ Usual starting dose is 16 mg QD. ▪ Candesartan can be administered QD or BID with total daily doses ranging from 8-32 mg. ▪ If BP is not controlled by candesartan alone, a diuretic may be added.	▪ Initial dosage is 150 mg QD with/without food. ▪ Patients may be titrated to 300 mg QD. ▪ A low dose of a diuretic may be added if BP is not controlled by irbesartan alone. ▪ Patients not adequately treated by the maximum dose of 300 mg QD are unlikely to derive additional benefit from a higher dose or BID dosing.	▪ Initial dosage is 50 mg QD with or without food. ▪ Losartan can be administered QD or BID with total daily doses ranging from 25-100 mg. ▪ If QD dosing is inadequate, a BID regimen at the same total daily dose or an increase in dose may give a more satisfactory response. ▪ If BP is not controlled by losartan alone, a low dose of a diuretic may be added.
FDA Labeled Indications	• Hypertension:	• Hypertension: • Nephropathy in type 2 diabetic patients: Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (greater than 300 mg/day) in patients with type 2 diabetes and hypertension. In this population, irbesartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).	• Hypertension: • Hypertensive patients with left ventricular hypertrophy (LVH) • Nephropathy in type 2 diabetic patients Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio greater than or equal to 300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, losartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation). • Indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy

Angiotensin II Receptor Blockers (ARBs)			
Characteristic	**Atacand (Candesartan)**	**Avapro (Irbesartan)**	**Cozaar (Losartan)**
Pediatric Labeling	No	No: but per package insert: Children less than 6 years of age: Safety and efficacy have not been established. Children 6 to 12 years of age: An initial dose of 75 mg once daily is reasonable. Titrate patients requiring further reduction in blood pressure to 150 mg once daily. Adolescents 13 to 16 years of age: An initial dose of 150 mg once daily is reasonable. Titrate patients requiring further reduction in blood pressure to 300 mg once daily. Higher doses are not recommended.	No
Other studied uses	Reduces microalbuminuria in Type 2 DM. (CALM study) Studies ongoing in CHF, development of hypertension in patients with high normal blood pressure, prevention of cognitive dysfunction in elderly with hypertension, diabetic nephropathy, prevention and progression of diabetic retinopathy in patients with types 1 and 2 DM.	Studies in reducing microalbuminuria in type 2 diabetes (IRMA-2 and IDNT)	Beneficial effects on CHF morbidity and mortality (ACE inhibitors still preferred); Beneficial effects on CHF morbidity and mortality after myocardial infarction (ACE inhibitors still preferred).(OPTIMAAL Study).
Contraindications	• Hypersensitivity to any component of these products • Pregnancy • Renal artery stenosis (solitary kidney or bilateral disease)		
Drug interactions	• Coadministration of digoxin and Micardis® (telmisartan) results in a 49 to 50% increase in the digoxin peak plasma concentration and a 13 to 20% increase in the trough digoxin concentration. • Coadministration of Micardis® telmisartan and warfarin for 10 days resulted in a slight decrease in the warfarin trough plasma concentration. However, a change in the International Normalized Ratio (INR) did not occur .		

Angiotensin II Receptor Blockers (ARBs)			
Characteristic	**Atacand (Candesartan)**	**Avapro (Irbesartan)**	**Cozaar (Losartan)**
Major Aes / Warnings	▪ One advantage of this class is its excellent tolerability and low side effect profile. In controlled clinical trials, discontinuation of therapy because of adverse reactions was required in 2.3% of patients treated with losartan or valsartan, 2.8% with telmisartan, 3.3% with irbesartan and 2.4% with candesartan vs 3.7%, 2%, 6.1%, 4.5%, and 3.4%, respectively, given placebo. ▪ When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue losartan as soon as possible. ▪ Cough: Although the incidence of cough is significantly higher in patients receiving ACEI as compared to ARBII therapy. ▪ Angioedema: Use caution if a patient has a history of angioedema with ACE inhibitor usage. ARBs have had angioedema as a side effect noted in the literature.		
Dosage adjustment in key populations	▪ As a class: Use a lower starting dose in patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur. ▪ Elderly: No dosage adjustment is necessary when initiating ARBIIs in the elderly. No overall differences in effectiveness or safety of candesartan, irbesartan, losartan, olmesartan, eprosartan or telmisartan were observed between elderly patients and younger patients, but greater sensitivity of some older individuals can not be ruled out. ▪ African American population appears to respond to a lesser degree to the antihypertensive effects of ARBIIs than the Caucasian population. Hepatic impairment: Candesartan: no dosage adjustment necessary, Olmesartan: AUC levels increased by 60% in patients with impairment, Valsartan: In general no dosage adjustment is required; exercise caution, Irbesartan: no dosage adjustment necessary, Telmisartan: dosage adjustment required in patients with hepatic impairment, Losartan: Lower starting dose is recommended in patients with hepatic insufficiency, Eprosartan: No dosage adjustment is required.		
Pipeline Agents/Future Products	*See last page of Class Review*		
Summary/Efficacy	*See last page of Class Review*		

Angiotensin II Receptor Blockers (ARBs)			
Characteristic	**Diovan (Valsartan)**	**Micardis (Telmisartan)**	**Teveten (Eprosartan)**
Pharmacology	Losartan, candesartan, irbesartan, telmisartan, olmesartan and valsartan are angiotensin II receptor (type AT1) antagonists. Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [ACE; kininase II]) is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin-aldosterone system (RAAS), and an important component in the pathophysiology of HTN. Its effects are vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Angiotensin II receptor antagonists (ARBs) block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor in many tissues (adrenal gland, heart, brain, fetus and injured tissues), but it is not known to be associated with cardiovascular homeostasis. A third receptor AT3 has been discovered in the neuroblastoma cells in amphibians, and a fourth, AT4 (found in brain, heart, lung, prostate, kidney, adrenal gland of humans and mice)is thought to be a renal vasodilator and is thought to stimulate plasminogen activator inhibitor 1. ARBs have a selective affinity for the AT1 receptor. ARBs do not inhibit ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. ARBs do not affect the response to bradykinin, whereas ACE inhibitors do increase the response. In spite of the decreasing aldosterone secretion, ARBs have very little effect on serum potassium.		
Generic available?	No	No	No
Manufacturer	Novartis	Boehringer Ingelheim	Biovail
Date of FDA approval	December 23, 1996.	November 10, 1998.	October 22, 1999.
Dosage forms / route of admin.	Diovan Capsules: 40mg. 80 mg, 160 mg, 320 mg **With HCTZ:** (valsartan/HCTZ) Diovan HCT: 80/12.5,160/12.5, 160/25mg	Micardis Tablets: 20mg, 40 mg, 80 mg **With HCTZ:** (telmisartan/HCTZ) Micardis HCT: 40/12.5, 80/12.5mg	Teveten Tablet: 400 mg, 600 mg **With HCTZ:** (eprosartan/HCTZ) Teveten HCT: 600/12.5, 600/25 mg

Angiotensin II Receptor Blockers (ARBs)			
Characteristic	**Diovan (Valsartan)**	**Micardis (Telmisartan)**	**Teveten (Eprosartan)**
Dosing frequency	▪ Starting dose is 80 mg QD, with or without food. ▪ Valsartan may be used over a dose range of 80-320 mg QD. ▪ If additional antihypertensive effect is required, the dosage may be increased to 160-320 mg or a diuretic may be added. ▪ Addition of a diuretic has a greater effect than dose increases beyond 80 mg.	▪ Starting dose is 40 mg/day. ▪ Blood pressure response is dose-related over the range of 20-80 mg. ▪ May be administered with or without food. ▪ When additional blood reduction beyond that achieved with 80 mg is required, a diuretic may be added.	▪ Starting dosage is 600 mg QD. ▪ Eprosartan can also be administered QD or BID with total daily doses ranging from 400-800 mg. ▪ If the antihypertensive effect measured at trough using once-daily dosing is inadequate, a BID regimen at the same total daily dose or an increase in dose may give a more satisfactory response. ▪ Eprosartan may be used in combination with other antihypertensive agents.
Indications	• Hypertension: Treatment of hypertension alone or in combination with other antihypertensive agents. • Heart failure: Treatment of heart failure (NYHA class II to IV) in patients who are intolerant of angiotensin-converting enzyme (ACE) inhibitors.	• Hypertension	• Hypertension:
Pediatric Labeling	No	No	No
Other studied uses	Reduces microalbuminuria in type 2 DM. (MARVAL STUDY) Study ongoing in CHF after myocardial infarction, diabetic nephropathy in type 2 DM, diabetes onset in patients with impaired glucose.	Studies ongoing in diabetic nephropathy, prevention of cardiovascular morbidity and mortality in high-risk patients	
Contraindications	• Hypersensitivity to any component of these products • Pregnancy • Renal artery stenosis (solitary kidney or bilateral disease)		
Drug interactions	• Coadministration of digoxin and Micardis® (telmisartan) results in a 49 to 50% increase in the digoxin peak plasma concentration and a 13 to 20% increase in the trough digoxin concentration. • Coadministration of Micardis® telmisartan and warfarin for 10 days resulted in a slight decrease in the warfarin trough plasma concentration. However, a change in the International Normalized Ratio (INR) did not occur .		

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Major Aes / Warnings	▪ One advantage of this class is its excellent tolerability and low side effect profile. In controlled clinical trials, discontinuation of therapy because of adverse reactions was required in 2.3% of patients treated with losartan or valsartan, 2.8% with telmisartan, 3.3% with irbesartan and 2.4% with candesartan vs 3.7%, 2%, 6.1%, 4.5%, and 3.4%, respectively, given placebo. ▪ When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue losartan as soon as possible. ▪ Cough: Although the incidence of cough is significantly higher in patients receiving ACEI as compared to ARBII therapy. ▪ Angioedema: Use caution if a patient has a history of angioedema with ACE inhibitor usage. ARBs have had angioedema as a side effect noted in the literature.		
Dosage adjustment in key populations	▪ As a class: Use a lower starting dose in patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur. ▪ Elderly: No dosage adjustment is necessary when initiating ARBIIs in the elderly. No overall differences in effectiveness or safety of candesartan, irbesartan, losartan, olmesartan, eprosartan or telmisartan were observed between elderly patients and younger patients, but greater sensitivity of some older individuals can not be ruled out. ▪ African American population appears to respond to a lesser degree to the antihypertensive effects of ARBIIs than the Caucasian population. Hepatic impairment: Candesartan: no dosage adjustment necessary, Olmesartan: AUC levels increased by 60% in patients with impairment, Valsartan: In general no dosage adjustment is required; exercise caution, Irbesartan: no dosage adjustment necessary, Telmisartan: dosage adjustment required in patients with hepatic impairment, Losartan: Lower starting dose is recommended in patients with hepatic insufficiency, Eprosartan: No dosage adjustment is required.		
Pipeline Agents/Future Products	*See last page of Class Review*		
Summary/Efficacy	*See last page of Class Review*		

	Angiotensin II Receptor Blockers (ARBs)
Characteristic	**Benicar** (Olmesartan)
Pharmacology	Losartan, candesartan, irbesartan, telmisartan, olmesartan and valsartan are angiotensin II receptor (type AT1) antagonists. Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [ACE; kininase II]) is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin-aldosterone system (RAAS), and an important component in the pathophysiology of HTN. Its effects are vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Angiotensin II receptor antagonists (ARBs) block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor in many tissues (adrenal gland, heart, brain, fetus and injured tissues), but it is not known to be associated with cardiovascular homeostasis. A third receptor AT3 has been discovered in the neuroblastoma cells in amphibians, and a fourth, AT4 (found in brain, heart, lung, prostate, kidney, adrenal gland of humans and mice)is thought to be a renal vasodilator and is thought to stimulate plasminogen activator inhibitor 1. ARBs have a selective affinity for the AT1 receptor. ARBs do not inhibit ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. ARBs do not affect the response to bradykinin, whereas ACE inhibitors do increase the response. In spite of the decreasing aldosterone secretion, ARBs have very little effect on serum potassium.
Generic available?	No
Manufaturer	Sankyo
Date of FDA approval	April 26, 2003
Dosage forms / route of admin.	**Tablets** 5, 20, 40 mg **With HCTZ:** (olmisartan/HCTZ) Benicar HCT: 20/12.5, 40/12.5, 40/25mg
Dosing frequency	Dosage must be individualized. The usual recommended starting dose is 20 mg once daily with or without food when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily. If blood pressure is not controlled by olmesartan alone, a diuretic may be added. Olmesartan may be administered with other antihypertensive agents.
Indications	Hypertension:
Pediatric Labeling	No

	Angiotensin II Receptor Blockers (ARBs)
Characteristic	**Benicar** (Olmesartan)
Other studied uses	• Heart failure • Reducing the rates of progression of renal disease and adverse clinical sequelae in hypertensive patients with diabetic nephropathy caused by type II diabetes • Reduction of BP in ISH
Contraindications	• Hypersensitivity to any component of these products • Pregnancy • Renal artery stenosis (solitary kidney or bilateral disease)
Drug interactions	• Coadministration of digoxin and Micardis® (telmisartan) results in a 49 to 50% increase in the digoxin peak plasma concentration and a 13 to 20% increase in the trough digoxin concentration. • Coadministration of Micardis® telmisartan and warfarin for 10 days resulted in a slight decrease in the warfarin trough plasma concentration. However, a change in the International Normalized Ratio (INR) did not occur .
Major Aes / Warnings	▪ One advantage of this class is its excellent tolerability and low side effect profile. In controlled clinical trials, discontinuation of therapy because of adverse reactions was required in 2.3% of patients treated with losartan or valsartan, 2.8% with telmisartan, 3.3% with irbesartan and 2.4% with candesartan vs 3.7%, 2%, 6.1%, 4.5%, and 3.4%, respectively, given placebo. ▪ When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue losartan as soon as possible. ▪ Cough: Although the incidence of cough is significantly higher in patients receiving ACEI as compared to ARBII therapy. ▪ Angioedema: Use caution if a patient has a history of angioedema with ACE inhibitor usage. ARBs have had angioedema as a side effect noted in the literature.
Dosage adjustment in key populations	▪ As a class: Use a lower starting dose in patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur. ▪ Elderly: No dosage adjustment is necessary when initiating ARBIIs in the elderly. No overall differences in effectiveness or safety of candesartan, irbesartan, losartan, olmesartan, eprosartan or telmisartan were observed between elderly patients and younger patients, but greater sensitivity of some older individuals can not be ruled out. ▪ African American population appears to respond to a lesser degree to the antihypertensive effects of ARBIIs than the Caucasian population. Hepatic impairment: Candesartan: no dosage adjustment necessary, Olmesartan: AUC levels increased by 60% in patients with impairment, Valsartan: In general no dosage adjustment is required; exercise caution, Irbesartan: no dosage adjustment necessary, Telmisartan: dosage adjustment required in patients with hepatic impairment, Losartan: Lower starting dose is recommended in patients with hepatic insufficiency, Eprosartan: No dosage adjustment is required.
Pipeline	*See last page of Class Review*
Summary Efficacy	*See last page of Class Review*

ANGIOTENSIN II RECEPTOR BLOCKER (ARB) SUMMARY

Pipeline Agents/Future Products	Future products in this area mainly involve development of agents that alter the renin-angiotensin-aldosterone axis in order to decrease cardiovascular outcomes ▪ BK B2 receptor agonists: The nonapeptide bradykinin (BK) stimulates BK B(2) receptors. In various animal models and in humans it has been shown that the stimulation of BK B(2) receptors is not only implicated in the pathogenesis of inflammation, pain and tissue injury but also in powerful cardioprotective mechanisms. None of the currently known agonists of BK B(2) receptors--RMP-7 (lobradamil, Cereport; Alkermes), JMV-1116 (Fournier), FR-190997 (Fujisawa) and FR-191413 (Fujisawa)--have been selected for a clinical assessment in cardiovascular indications, but may once the it is known if there is a safe therapeutic window between potential cardioprotective and pro-inflammatory effects following BK B(2) receptor agonism. ▪ Endothelin receptor antagonists: Tracleer® (bosentan) marketed for pulmonary hypertension ▪ Vasopressin receptor antagonists: Vasopressin appears to adversely effect hemodynamics and cardiac remodeling, while potentiating the effects of norepinephrine and angiotensin II. The selective V(2) and dual V(1a)/V(2) receptor antagonists tolvaptan and conivaptan (Yamanouchi) respectively, substantially increase free water excretion and plasma osmolality, reduce body weight, improve symptoms of congestion, and moderately increase serum sodium concentrations in patients with heart failure who present with symptoms of fluid overload. ▪ Dual ACE/NEP inhibitor drugs (Vasopeptidase inhibitors): Drugs that possess the ability to inhibit simultaneously the membrane-bound zinc metalloproteases, angiotensin-converting enzyme (ACE), and the neutral endopeptidase EC 3.4.24.11 (NEP). 3. Omapatrilat (BMS), the most studied dual ACE/NEPinhibitor, had its initial NDA to the US FDA withdrawn by the MFT due to the high incidence of angioedema seen in ACE/NEP inhibitors over traditional ACEIs. At that time, BMS initiated large-scale trials to address this issue (OCTAVE, OPERA and OVERTURE). Thus far, OCTAVE has confirmed the antihypertensive efficacy of omapatrilat, but the rate of angioedema was three-fold higher than that normally seen with ACEIs. In OVERTURE, the rate of angioedema was comparable to that of enalapril, but omapatrilat was not superior to enalapril as antihypertensive therapy. 4. Samapatrilat: is another dual ACE/NEP inhibitor that is in Phase II clinical trials The future of this class of drugs will depend upon the tolerability of their side-effect profile and if high risk patients (patients at risk for angioedema) can be identified and excluded.

ANGIOTENSIN II RECEPTOR BLOCKER (ARB) SUMMARY	
Summary/Efficacy	▪ There is a small uricosuric effect with losartan (Cozaar®) leading to a minimal decrease in serum uric acid (mean decrease < 0.4 mg/dl) during chronic oral administration (this is due to a specific effect of losartan (Cozaar®) on urate transport in the renal proximal tubule and is independent of its effects on angiotensin II receptor blockade. ▪ Hyperuricemia has been seen with candesartan (Atacand®) in rare instances ▪ All ARBs are structurally related to Losartan (Cozaar®) except for Eprosartan (Teveten®) ▪ It has been proposed that ARBs differ in the way that they block AT_1 in that they may exhibit insurmontable (noncoompetitive) or surmontable (competitive) binding. Insurmontable blockade, however, is difficult to achieve at the doses used clinically, and thus it is believed that all ARBs are surmontable (competitive) but have a very slow dissociation rate from the receptor. This kinetic distinction has not been shown to result in clinical differences when ARBs are used in therapeutic dosages. ▪ Differences in half-lives are difficult to interpret as plasma half-lives only roughly approximate duration of action. A more accurate reflection of duration of action would be to measure the strength or amount of tissue based AT_1 binding; however , this is not clinically feasible. ▪ Teveten® appears to have a greater affinity for pre-synaptic AT_1 receptors which may account for its proposed ability to decrease sympathetic nervous system output. ▪ When used in combination with a diuretic, all ARBs experience a synergistic response with this combination in decreasing blood pressure. ▪ Meta analysis done by Conlin et al (abstract attached) showed comparable antihypertensive efficacy of Cozaar ® , Diovan® , Avapro® and Atacand® when administered at their recommended dosages. The meta-analysis also showed that all four agents exhibited a near flat dose-response curve when given at recommended dosages; however, the addition of a low-dose diuretic produced a synergistic response in the reduction of BP. ▪ A second meta analysis done by Conlin et al (abstract attached) evaluated all ARBS but olmesartan and concluded there is little clinically significant difference in efficacy between the six ARBs in the treatment of hypertesnion. ▪ American Diabetes Association Position Statement on diabetic nephropathy from January 2002 stated that in hypertensive patients with type 2 diabetes with microalbuminuria or clinical albuminuria, ARBs are the initial agents of choice. In hypertensive and nonhypertensive type 1 diabetic patients with microalbuminuria or clinical albuminuria, ACEI are the initial agents of choice. The ADA states that if one class is not tolerated, the other class should be substituted. Specific agents were not chosen by the ADA. ▪ Currently, published long term studies indicate the utility of ACE inhibitors in diabetes, CHF and post-MI. ARBs are indicated in CHF patients who are intolerant to ACEI. ▪ Only Avapro® and Cozaar® are FDA labeled for the treatment of diabetic nephropathy in type 2 diabetes; however, there are substantial studies for Atacand® and Diovan® for this indication, and ongoing studies for Micardis® and Benicar®.

ANGIOTENSIN II RECEPTOR BLOCKER (ARB) SUMMARY

General Pharmacokinetics

Kinetics	Atacand (Candesartan)	Avapro (Irbesartan)	Cozaar (Losartan)	Diovan (Valsartan)	Micardis (Telmisartan)	Teveten (Eprosartan)	Benicar (Olmesartan)
ProDrug	Yes	No	Yes	No	No	No	No
Bioavailability	15%	60-80%	33%	25%	42-58%	13%	26%
Active Metabolite	Yes: TCV 116 Yes: CV11974	No	Yes: EXP 3174	No	No	No	No
Half-Life (hours)	3.5-4 hours	11-15 hours	2 h 6-9 h for active metabolite(s)	9 hours	24 hours	5-7 hours	13 hours
Protein binding	99.5% (CV11974)	90%	98.7%, (99.8%)	95%	>99%	98%	99%
Renal Clearance %	60	1	10	30	1	30	10
Hepatic Clearance %	40	99	90	70	99	70	90

Angiotensin II Antagonists in the Treatment of Hypertension: More Similarities Than Differences.

Conlin PR.
J Clin Hypertens (Greenwich). 2000 Jul;2(4):253-257.

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As the class of angiotensin-II antagonists expands, it becomes relevant to know if there are differences in antihypertensive efficacy among the various agents. Prior to regulatory approval, all agents have been evaluated vs. placebo. We excerpted the placebo-corrected reductions in diastolic blood pressure for angiotensin II antagonist monotherapy, using objective regulatory review data from the U.S. product circulars. Both systolic and diastolic blood pressure reductions were very similar. In 25 randomized clinical trials that compared angiotensin II antagonists to other classes, equivalent antihypertensive efficacy was demonstrated at recommended doses. Data pooled from 51 clinical trials showed comparable weighted average diastolic blood pressure reductions (not placebo-corrected) for monotherapy with losartan, valsartan, irbesartan, candesartan, and telmisartan. Reductions in systolic blood pressure paralleled the changes in diastolic blood pressure. Somewhat smaller responses were observed with eprosartan, although this was based on fewer patients. Thus, there appears to be little clinically significant difference in blood pressure efficacy among the six marketed angiotensin II antagonists in the treatment of hypertension.

Angiotensin II antagonists for hypertension: are there differences in efficacy?

Conlin PR, Spence JD, Williams B, Ribeiro AB, Saito I, Benedict C, Bunt AM.

Am J Hypertens. 2000 Apr;13(4 Pt 1):418-26.

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We compared the antihypertensive efficacy of available drugs in the new angiotensin-II-antagonist (AIIA) class. The antihypertensive efficacy of losartan, valsartan, irbesartan, and candesartan was evaluated from randomized controlled trials (RCT) by performing a metaanalysis of 43 published RCT. These trials involved AIIA compared with placebo, other antihypertensive classes, and direct comparisons between AIIA. A weighted-average for diastolic and systolic blood pressure reduction with AIIA monotherapy, dose titration, and with addition of low-dose hydrochlorothiazide (HCTZ) were calculated. Weighted-average responder rates were also determined. The metaanalysis assessed a total of 11,281 patients. The absolute weighted-average reductions in diastolic (8.2 to 8.9 mm Hg) and systolic (10.4 to 11.8 mm Hg) blood pressure reductions (not placebo-corrected) for AIIA monotherapy were comparable for all AIIA. Responder rates for AIIA monotherapy were 48% to 55%. Dose titration resulted in slightly greater blood pressure reduction and an increase in responder rates to 53% to 63%. AIIA/hydrochlorothiazide combinations produced substantially greater reduction in systolic (16.1 to 20.6 mm Hg) and diastolic (9.9 to 13.6 mm Hg) blood pressure reductions than AIIA monotherapy and responder rates for AIIA/HCTZ combinations were 56% to 70%. This comprehensive analysis shows comparable antihypertensive efficacy within the AIIA class, a near-flat AIIA-dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ.

Debate: angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers--a gap in evidence-based medicine.

Ball SG, White WB.
Am J Cardiol. 2003 May 22;91(10A):15G-21G.

Department of Cardiovascular Medicine, University of Leeds, Leeds, United Kingdom.

In this article, 2 leading physicians debate the strength of outcome data on the efficacy of angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs) for reducing the incidence of cardiovascular, cerebrovascular, and renovascular events. Dr. Stephen G. Ball notes that the efficacy of ACE inhibitors for reducing the risk for myocardial infarction independent of their effects on blood pressure is controversial. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril treatment in high-risk patients was associated with a 20% reduction in the risk for myocardial infarction; mean reduction in blood pressure was 3 mm Hg for systolic blood pressure and 1 mm Hg for diastolic blood pressure. The HOPE investigators propose that the 20% reduction was much greater than would be expected based on the observed blood pressure reduction. However, a meta-regression analysis of blood pressure reduction in >20 antihypertensive therapy outcome trials found that the reduction in myocardial infarction risk with ramipril observed in HOPE was consistent with the modest blood pressure reduction seen with that agent. Nevertheless, there are convincing data for prevention of myocardial infarction with ACE inhibitors in patients with heart failure, including those with heart failure after myocardial infarction, as well as supportive evidence from studies in patients with diabetes mellitus and concomitant hypertension. On the other hand, Dr. William B. White takes the position that ARBs are well-tolerated antihypertensive agents that specifically antagonize the angiotensin II type 1 (AT(1)) receptor and provide a more complete block of the pathologic effects of angiotensin II-which are mediated via the AT(1) receptor-than ACE inhibitors. The Evaluation of Losartan in the Elderly (ELITE) II study and the Valsartan Heart Failure Trial (ValHeFT) suggest that ARBs reduce the risk for mortality in patients with congestive heart failure. The Losartan Intervention for Endpoint (LIFE) Reduction in Hypertension trial also demonstrated beneficial effects of ARBs in the prevention of stroke events. The Irbesartan in Patients with Diabetes and Microalbuminuria (IRMA) study, the Irbesartan Diabetic Nephropathy Trial (IDNT), and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated significant reductions in the rate of progression of renal disease in patients receiving ARBs, independent of effects on blood pressure. These data support the use of ARBs, in addition to the standard of care, in hypertensive patients with heart failure who are intolerant of ACE inhibitors, and also provide compelling evidence for their use in patients with hypertension and type 2 diabetes.

Comparison of the antagonistic effects of different angiotensin II receptor blockers in human coronary arteries.

Pantev E, Stenman E, Wackenfors A, Edvinsson L, Malmsjo M.
Eur J Heart Fail. 2002 Dec;4(6):699-705.

Division of Experimental Vascular Research, Department of Internal Medicine, Lund University Hospital, Lund, Sweden.

BACKGROUND: Angiotensin II (Ang II) is a potent vasoconstrictor and a deleterious factor in cardiovascular pathophysiology. Ang II receptor blockers (ARBs) have recently been introduced into clinical practice for treatment of hypertension and congestive heart failure. AIMS: This study was undertaken to evaluate the inhibitory effects of ARBs on vasoconstriction in humans. METHODS: Vasomotor tone was analyzed in endothelium denuded, human coronary artery (HCA) segments. Ang II type 1 (AT(1)) and type 2 (AT(2)) receptor mRNA expression was examined by reverse transcriptase-polymerase chain reaction (RT-PCR). RESULTS: Ang II was a potent vasoconstrictor (pEC(50) = 7.7). At 1 nM of the AT(1) receptor antagonists, candesartan and valsartan, the maximum contraction was depressed to 57 and 50% of Ang II, respectively, indicating insurmountability. Although generally considered surmountable, the presence of 100 nM losartan elicited a depression of the Ang II response to 32%. Its active metabolite, EXP 3174 (1 nM), abolished the Ang II contraction. The AT(1) receptor antagonists had the following order of blocking effect; EXP 3174 > candesartan = valsartan > losartan. The AT(2) receptor antagonist, PD 123319 (100 nM) significantly attenuated the Ang II contraction (E(max) = 62% of Ang II). RT-PCR of HCA smooth muscle cells demonstrated expression of both AT(1) and AT(2) receptor mRNA. CONCLUSIONS: Ang II contraction in HCA is mediated mainly by AT(1) but also involves AT(2) receptors. The active metabolite of losartan, EXP 3174, is the most efficacious AT(1) receptor antagonist in HCA. Copyright 2002 European Society of Cardiology

Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from a multicenter, randomized, double-blind, 12-week trial.

Elliott WJ, Calhoun DA, DeLucca PT, Gazdick LP, Kerns DE, Zeldin RK.
Clin Ther. 2001 Aug;23(8):1166-79.

Rush-Presbyterian/St Luke's Medical Center, Chicago, Illinois, USA.

BACKGROUND: Losartan, the first of the angiotensin II receptor blockers (ARBs) to be introduced, has been studied extensively in comparison with other classes of antihypertensive agents. Less research has been conducted on the efficacy and tolerability of losartan compared with that of other ARBs. OBJECTIVE: This randomized, multicenter, double-blind, parallel-group equivalence study was conducted to compare the antihypertensive efficacy and tolerability of a once-daily regimen of losartan with that of valsartan. METHODS: Patients > or = 21 years of age with mild to moderate hypertension, defined as a trough sitting diastolic blood pressure (SiDBP) between 95 and 115 mm Hg, were randomized to receive once-daily losartan (50 mg) or valsartan (80 mg) for 12 weeks. At the end of the sixth treatment week, patients in both groups with trough SiDBP > or = 90 mm Hg had their dose doubled for the remainder of the treatment period. Analysis of variance was used to compare treatment groups with respect to change in mean trough SiDBP from baseline to week 12. Within-treatment changes were analyzed using the paired t test. With at least 220 patients per treatment group, the study had 90% power to place a 90% CI on the difference between losartan and valsartan in SiDBP within the equivalence interval of +/- 2.5 mm Hg. RESULTS: A total of 495 patients were randomized, 247 to the losartan group and 248 to the valsartan group: 456 patients completed the study. Adjusted mean change from baseline values for trough SiDBP atthe end of 12 weeks of treatment were significantly different (P < 0.001) from zero in both the losartan group (-9.9 mm Hg) and the valsartan group (-10.1 mm Hg). At week 12, losartan was as effective as valsartan in lowering SiDBP, with a between-group difference of 0.2 mm Hg (90% CI, -1.3 to 1.7; P = 0.827). At week 6, the difference in SiDBP between groups was -1.3 mm Hg (90% CI, -2.7 to 0.0; P = 0.106). A similar pattern of results was obtained at weeks 6 and 12 for sitting systolic blood pressure. The percentage of patients reaching the SiDBP goal at week 6 (46% [112/2411 losartan; 42% [103/245] valsartan) and week 12 (57% [139/243] losartan; 59% [145/245] valsartan) was not significantly different between the treatment groups. Both losartan and valsartan were similarly well tolerated. Over the 12 weeks, the laboratory profiles of the 2 drugs were similar except for serum uric acid levels, which decreased from 6.0 to 5.7 mg/dL in the losartan group and increased from 5.9 to 6.0 mg/dL in the valsartan group (P = 0.001 for between-treatment difference). CONCLUSIONS: At starting and titrated doses, losartan and valsartan are similarly effective in reducing blood pressure in patients with mild to moderate hypertension. Losartan, but not valsartan, was associated with a decrease in serum uric acid levels.

VALUE trial: Long-term blood pressure trends in 13,449 patients with hypertension and high cardiovascular risk.

Julius S, Kjeldsen SE, Brunner H, Hansson L, Platt F, Ekman S, Laragh JH, McInnes G, Schork AM, Smith B, Weber M, Zanchetti A; VALUE Trial.

Am J Hypertens. 2003 Jul;16(7):544-8.

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BACKGROUND: The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study compares cardiovascular outcomes in 15,314 eligible patients from 31 countries randomized to valsartan or amlodipine-based treatment. METHODS: The blood pressure (BP) trends are analyzed in 13,449 of VALUE study patients who had baseline BP and 24 months BP and treatment data. RESULTS: In a cohort of 12,570 patients, baseline 24 and 30 months BP, but not 30 months treatment data, were available. Of 13,449 patients, 92% (N = 12,398) received antihypertensive therapy at baseline. The baseline BP was 153.5/86.9 mm Hg in treated compared to 168.1.8/95.3 mm Hg in 1051 untreated patients. After 6 months both groups had indistinguishable BP values. At 12 months the BP decreased to 141.2/82.9 mm Hg (P <.0001 for systolic BP and diastolic BP versus baseline), at 24 months to 139.1/80 mm Hg (P <.0001 v 12 months), and to 138/79 mm Hg at 30 months (P <.0001 v 24 months). The systolic BP control (<140 mm Hg) at 30 months increased from 21.9% at baseline to 62.2%, the diastolic BP (< 90 mm Hg) from 54.2% to 90.2% and the combined control (<140 and <90 mm Hg) from 18.9% to 60.5%. At 24 months 85.8% of patients were on protocol drugs: monotherapy = 39.7%, added hydrochlorothiazide = 26.6%, add-on drugs = 15.1%, and protocol drugs in nonstandard doses = 4.3%. CONCLUSIONS: The achieved BP control exceeds values reported in most published large-scale trials. The VALUE study is executed in regular clinical settings and 92% of the patients received antihypertensive drugs at baseline. When an explicit BP goal is set, and a treatment algorithm is provided, the physicians can achieve better control rates than in their regular practice.

Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect.

Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators.

Circulation. 2002 Aug 6;106(6):672-8.

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BACKGROUND: Elevated urine albumin excretion (UAER) is a modifiable risk factor for renal and cardiovascular disease in type 2 diabetes. Blockade of the renin-angiotensin system lowers UAER, but whether this effect is independent of blood pressure (BP) reduction remains controversial. The MicroAlbuminuria Reduction With VALsartan (MARVAL) study was designed to evaluate the BP-independent effect of valsartan on UAER in type 2 diabetic patients with microalbuminuria. METHODS AND RESULTS: Three hundred thirty-two patients with type 2 diabetes and microalbuminuria, with or without hypertension, were randomly assigned to 80 mg/d valsartan or 5 mg/d amlodipine for 24 weeks. A target BP of 135/85 mm Hg was aimed for by dose-doubling followed by addition of bendrofluazide and doxazosin whenever needed. The primary end point was the percent change in UAER from baseline to 24 weeks. The UAER at 24 weeks was 56% (95% CI, 49.6 to 63.0) of baseline with valsartan and 92% (95% CI, 81.7 to 103.7) of baseline with amlodipine, a highly significant between-group effect (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive subgroups. More patients reversed to normoalbuminuria with valsartan (29.9% versus 14.5%; P=0.001). Over the study period, BP reductions were similar between the two treatments (systolic/diastolic 11.2/6.6 mm Hg for valsartan, 11.6/6.5 mm Hg for amlodipine) and at no time point was there a between-group significant difference in BP values in either the hypertensive or the normotensive subgroup. CONCLUSIONS: For the same level of attained BP and the same degree of BP reduction, valsartan lowered UAER more effectively than amlodipine in patients with type 2 diabetes and microalbuminuria, including the subgroup with baseline normotension. This indicates a BP-independent antiproteinuric effect of valsartan.

Type 2 diabetes: RENAAL and IDNT--the emergence of new treatment options.

Sica DA, Bakris GL.

J Clin Hypertens (Greenwich). 2002 Jan-Feb;4(1):52-7.

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The Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT) are two recently reported trials with hard end points, conducted in patients in advanced stages of diabetic nephropathy. Two other studies--the Irbesartan Microalbuminuria Study (IRMA)-2 and the Microalbuminuria Reduction with Valsartan study (MARVAL)--were trials conducted in patients with type 2 diabetes with microalbuminuria, a cardiovascular risk factor associated with early-stage diabetic nephropathy. These trials all had a common theme--that is, does an angiotensin receptor blocker (ARB) interfere with the natural history of diabetic nephropathy in a blood pressure-independent fashion? Without question, the results of these trials legitimatize the use of the ARB class in forestalling the deterioration in renal function, which is almost inevitable in the patient with untreated diabetic nephropathy. These data can now be added to the vast array of evidence supporting angiotensin-converting enzyme (ACE) inhibitor use in patients with nephropathy associated with type 1 diabetes. It now appears a safe conclusion that the patient with diabetic nephropathy should receive therapy with an agent that interrupts the renin-angiotensin system. These studies have not resolved the question as to whether an ACE inhibitor or an ARB is the preferred agent in people with nephropathy from type 1 diabetes, though the optimal doses of these drugs remain to be determined. Head-to-head studies comparing ACE inhibitors to ARBs in diabetic nephropathy are not likely to occur, so it is unlikely that comparable information will be forthcoming with ACE inhibitors. An evidence-based therapeutic approach derived from these trials would argue for ARBs to be the foundation of therapy in the patient with type 2 diabetes and nephropathy.

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Comparisons in a competitive world. When is one drug superior to another?

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EDITORIAL

Thanks to innovations in pharmacology and drug delivery systems physicians continue to have access to antihypertensive agents that tend to be more efficacious, better tolerated, and more convenient to use than previous generations of treatment. But unless a drug is the first member of a new and exciting class, its potential advantages may not be immediately apparent to the majority of prescribing clinicians.

For this reason, one of the best methods for establishing the usefulness of a newly available product is to compare it with other well-known agents. If the new drug is the first of its type, then clearly the appropriate comparisons would be with already established treatments. In contemporary times, for example, comparisons with such market leaders as the calcium channel blocker amlodipine or the ACE inhibitor enalapril would be most helpful in defining the credentials of a new entity.[1]

Even more necessary are comparisons within a drug class, particularly when recent entries attempt to show superiority over the original flag bearer of the group. The angiotensin receptor antagonists are a good case in point, and the newer drugs in this class have sought to distinguish themselves from the innovator agent losartan.[2, 3 and 4] Setting up valid comparisons, though, is not always a simple business. For a start, it is possible just by chance that one drug might unexpectedly beat another in a head-to-head comparison, and for this reason the Food and Drug Administration (FDA) requires that statistically significant superiority must be demonstrated in two separate studies before such claims can be made publicly.

Study design issues

Even then there are difficulties, especially with selecting appropriate doses. The antihypertensive dose-response curves of the angiotensin receptor antagonists tend to be rather flat, so it is difficult to define the maximally effective dose for some agents. Unlike most of the earlier drug classes, the angiotensin receptor antagonists do not have dose-dependent side effect profiles that could provide practical upper limits on doses. This has compelled the designers of comparative trials within this drug class to depend on the FDA-approved labeling instructions for choosing doses, a rather arbitrary and not necessarily fair basis for setting up a comparative study.

Other design questions also can affect the fairness of the research: for instance, should the comparisons be based on fixed doses, or should titration of doses be employed? And if titration is used, should it be contingent upon achieving certain blood pressure goals, or should it be a forced titration to the maximum allowed doses of each of the drugs? The duration of treatment and even the demographic characteristics of the patients studied are other factors that could influence the outcome of studies.

In this issue of the Journal, Conlin et al have approached this problem in a different fashion.[5] They have performed a metaanalysis based on the 43 available published randomized controlled trials from which blood pressure efficacy data were available for the angiotensin receptor blockers losartan, valsartan, irbesartan, and candasartan. These trials included placebo-controlled studies and comparisons with other drug types as well as direct head-to-head comparisons within the angiotensin receptor blocker class.

Based on this experience in over 11,000 hypertensive patients, the authors have concluded that there is no meaningful efficacy difference among these agents, regardless of whether they are used as monotherapy or in combination with low doses of diuretics. For the reasons already discussed, it is clear that comparisons among rival drugs are likely to be contentious. And, despite its apparent broad base, even a metaanalysis cannot be the last word on the subject.

Problems of bias

The results of clinical investigation are generally only available through publications in the medical literature. Metaanalysis is particularly dependent on what is published and what meets the inclusion criteria best judged to answer the question being addressed. The report of the metaanalysis in this issue of the Journal, interesting and useful as it is, like all other similar projects, could incorporate only what has been published.

What is not published, of course, may be just as important as what can be retrieved from the literature, and could potentially lead to inadvertent bias or inaccuracy in the conclusions of a metaanalysis. Comparative studies of drug efficacy are likely to be good examples of unpublished information, particularly when the studies do not demonstrate the superiority anticipated by the sponsor of the research. These efforts, cynically, are sometimes referred to as failed studies. Non-publication, albeit with some justification, is sometimes blamed on the reluctance of editors to accept papers that do not show interesting or surprising results. It is possible, too, that a sponsor may initiate several comparative studies with a variety of investigators; if one of these studies succeeds in showing the hoped-for superiority, it is submitted for publication; whereas the other studies, which failed to do so, are conveniently forgotten. And even when a non-superiority study is published, it can also be misleading, for unless a protocol has been designed and powered to show equivalence it can be inappropriate to assume that the two agents have similar efficacy.

The very large national or international clinical trials with mortality and morbidity endpoints are so well known to a wide circle of experts, often including the FDA, that it is virtually impossible not to publish the results regardless of how they turn out. Usually such studies have a steering committee or an executive group of impartial experts who can guarantee the integrity of the process. No such safeguards, however, exist for the numerous smaller and more simple studies that often are conducted by single investigators or small multicenter groups.

One solution to this problem would be to establish a global Registry of Clinical Studies. Any research requiring approval by an Institutional Review Board—in essence, all or most studies performed in humans—would be filed with the Registry. The purpose of the Registry is not to preempt data, or for that matter to even make it available. That is the province of investigators. Simply, the Registry would document that a particular study was at least begun or contemplated. This would at least allow the medical and scientific community to have a reasonable sense of what has been taking place, while at the same time not taking away from the investigators their prerogative to publish all, some, or none of their findings.

This approach, or one with a similar intent, may serve an even higher purpose. After all, any patient who is asked to sign an informed consent to enter a clinical trial should be entitled to know that the risks and inconvenience they might experience are justified by the creation of information for the greater public good. Documentation of the intent and existence of such studies, even if they fail, or are never completed or even never truly begun, can help to satisfy this purpose.

Endpoints for hypertension studies

The current basis for establishing efficacy of an antihypertensive drug is to measure its effects at trough, by definition at the end of its dosing interval. This standard has been encouraged by the FDA but does not necessarily provide optimal data about a drug and its properties compared with other drugs. There are situations where the ratio of the efficacies at trough and peak may be more revealing and could possibly be more flattering to one drug than another. Ambulatory blood pressure monitoring provides far more information. This technique can demonstrate differences between drugs in their 24-hour antihypertensive efficacies even when their trough effects appear similar. Ambulatory monitoring can also compare the effects of drugs on the circadian pattern of blood pressure and allow efficacy comparisons to be made during critical periods of the day. For example, drugs that appear to have similar effects may, in fact, be shown to have different effects during the morning hours (typically 6:00 . to noon, when a disproportionate number of cardiovascular events take place) or during the final 2 or 4 hours of the dosing intervals.[6]

The effectiveness approach

Rather than comparing the efficacy of arbitrarily chosen fixed doses of drugs, might it not make more sense to compare their effectiveness in enabling clinicians to achieve target blood pressures? The JNC VI guidelines suggest that hypertensives have their blood pressures reduced to below 140/90 mmHg, and that more complex hypertension—particularly when diabetes mellitus is involved—should be treated to below 130/85 mmHg.[7] Reaching these targets with monotherapy is not likely to succeed in most patients, and two or more drugs will often be required. If this is so, wouldn't the appropriate comparative test among drugs be to determine which of them best serves as the effective cornerstone of an antiohypertensive regimen? Which drug allows blood pressure targets to be achieved most predictably, requiring the fewest number of additional drugs, and with minimal adverse effects? In a sense, the ability of a drug to work powerfully when combined with other agents may be at least as important as its own single agent efficacy.

Man does not live by blood pressure alone

Blood pressure is a straightforward and readily measured endpoint and so represents the most obvious basis for comparative studies. But outcomes of treatment with hypertension drugs can be classified into three types: short-term, of which blood pressure effects are the most obvious; intermediate outcomes, including such important surrogate measures as echocardiographic left ventricular muscle mass, arterial compliance, and proteinuria or renal function; and long-term outcomes, typically the effects of drugs on survival or major clinical events like strokes, myocardial infarctions, heart failure, or end stage renal failure.

Purists might argue that because effects on intermediate endpoints have not yet been convincingly linked to survival benefits they might not be an optimal basis for drug comparison. Even so, in choosing between two antihypertensive agents with similar blood pressure efficacies, most physicians would be inclined to select the one that displayed better evidence for desirable effects like proclaiming regression of left ventricular hypertrophy, decreasing arterial stiffness or reducing proteinuria.

The good news is that the angiotensin receptor antagonists, which are the focus of the metaanalysis by Conlin et al,[5] are now the primary drugs in ongoing morbidity and mortality clinical trials in patients with high risk hypertension. Admittedly, these are not head-to-head comparisons among members of this class, nor do these major studies share identical designs. But the bragging rights that would go with a documented ability to prevent major events should enable any of the agents involved in these trials to prosper in the competitive world of antihypertensive drugs.

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Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Adalat, Procardia, Adalat CC, Procardia XL, Nifedical XL (Nifedipine)**	**Cardene, Cardene SR, (Nicardipine)**	**DynaCirc, DynaCirc Cr, (Isradipine)**
Pharmacology	Dihydropyridine calcium channel blockers inhibit calcium ions from entering the “slow channels” or select voltage-senstivie areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina. Nifedipine and related dihydropyridines do not have significant direct effects on the atrioventricular conduction system or sinoatrial node at normal doses, and therefore do not have *direct* effects on conduction or automaticity.The dihydropyridines can cause reflex increases in heart rate because of their potent vasodilating effects. Vasodilatation of arterial resistance vessels causes a reflex increase in sympathetic response. Dihydropyridines have very modest negative inotropic effects. Any weak direct negative inotropic effect of the drug is overwhelmed by the strong reflex sympathetic response. The overall hemodynamic effect is a drop in blood pressure, an increase in heart rate and contractility, and an increase in cardiac output.		
Generic formulation available?	Yes	Cardene: Yes, available generically Cardene SR: Brand only	No
Date of FDA Approval	**Immediate Release:** available generically **Controlled Release:** available generically	**Immediate Release:** December 21, 1988 **Controlled Release:** Feb. 21, 1992	**Immediate Release:** December 20, 1990 **Controlled Release:** June 1, 1994
Manufacturer	▪ multiple	▪ Roche	Reliant
Dosage forms available	▪ Adalat, Procardia Capsules: 10,20mg ▪ Adalat CC, Procardia XL Tablets, sustained release: 30, 60, 90 mg ▪ Nifedical XL Tablets, extended-release: ▪ 30, 60 mg	▪ Cardene Capsules: 20, 30 mg ▪ Cardene SR Capsules, sustained release: 30, 45, 60 mg ▪ Cardene Injection IV 2.5mg/ml	▪ DynaCirc Capsules: 2.5, 5 mg ▪ DynaCirc CR Tablets, controlled release: 5, 10 mg
Dosing frequency	▪ Nifedipine IR: TID to QID ▪ Nifedipine SR: QD	▪ Nicardipine IR: TID ▪ Nicardipine SR: BID	▪ Isradipine: BID ▪ Isradipine CR: QD

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Adalat, Procardia, Adalat CC, Procardia XL, Nifedical XL (Nifedipine)**	**Cardene, Cardene SR, (Nicardipine)**	**DynaCirc, DynaCirc Cr, (Isradipine)**
Generalized dosing guidelines	**Immediate Release Capsules:** 10 mg 3 times/day; usual range is 10 to 20mg 3 times/day. Some patients, especially those with coronary artery spasm, respond only to higher doses, more frequent administration, or both. In such patients, 20 to 30 mg 3 or 4 times/day may be effective. Doses above 120 mg/day are rarely necessary. More than 180 mg/day is not recommended. **Procardia XL and Nifedical XL:** 30 or 60 mg once daily. Titration to doses above 120 mg is not recommended. **Adalat CC (hypertension):** • Administer once daily on an empty stomach. In general, titrate over a 7- to 14-day period, starting with 30mg once daily. Base upward titration on therapeutic efficacy and safety. Usual maintenance dose is 30 to 60 mg once daily. Titration to doses above 90 mg/day is not recommended	**Angina (immediate-release only):** Individualize dosage. Usual initial dose is 20 mg 3 times/day (range, 20 to 40 mg 3 times/day). Allow at least 3 days before increasing dose to ensure achievement of steady-state plasma drug concentrations. **Hypertension:** Individualize dosage per dosage formulation **Immediate-release:** Initial dose is 20 mg 3 times daily (range, 20 to 40mg 3 times daily). **Sustained-release:** Initial dose is 30 mg twice daily. Effective doses have ranged from 30 to 60 mg twice daily. The total daily dose of immediate-release nicardipine may not be a useful guide in judging the effective dose of the sustained-release form. Titrate patients currently receiving the immediate-release form with the sustained-release form starting at their current total daily dose of immediate-release nicardipine, then re-examine.	**DynaCirc Immediate Release:** The recommended initial dose is 2.5 mg twice daily alone or in combination with a thiazide diuretic.The dose may be adjusted in increments of 5mg/day at 2- to 4-week intervals up to a maximum of 20mg/day. No additional response to doses above 10mg/day and adverse effects are increased in frequency above 10mg/day. **DynaCirc CR:** Recommended initial dose is 5 mg once daily alone or in combination with a thiazide diuretic. BP reduction is maintained for at least 24 hours following drug administration. If necessary, the dose may be adjusted in increments of 5 mg at 2- to 4-week intervals up to a maximum dose of 20 mg/day. Adverse experiences are increased in frequency above 10 mg/day. **Special populations:** The bioavailability of isradipine (increased AUC)is increased in elderly patients (above 65 years of age), patients with hepatic functional impairment, and patients with mild renal impairment. Ordinarily, the starting dose for these patients should be 2.5 mg twice daily (immediate-release)or 5 mg once daily (controlled-release).
FDA labeled Indications	• Vasospastic angina (except **Adalat CC**): • Chronic stable angina (except **Adalat CC**): • Hypertension:	• Chronic stable (effort-associated) angina • Hypertension	▪ Hypertension:

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Adalat, Procardia, Adalat CC, Procardia XL, Nifedical XL (Nifedipine)**	**Cardene, Cardene SR, (Nicardipine)**	**DynaCirc, DynaCirc Cr, (Isradipine)**
Pediatric Labeling	Not FDA labeled for children Nifedipine is not recommended or FDA approved for use in pediatric aged patients. However, unapproved dosage guidelines include: Nifedipine extended-release dosage forms for HTN: Initial dose, 0.25 mg/kg/day in one or two doses.Usual dose, 0.25 to 0.5 mg/kg/day in one or two doses.Max dose, 3mg/kg/day up to 180 milligrams per DAY in one or two doses ER Tablets must be swallowed whole and are generally too large for use by small children. Twice daily administration may be needed in children to obtain full 24-hour blood pressure control	Not FDA labeled for children.Usual dose, 20 to 30 mg every 8 hours.	Not FDA labeled for children Specific dosing guidelines are not published; not FDA approved; however, suspension may be compounded for infants and young children. The standard-release dosage form has shorter duration (6 to 8 hours) of effect in pediatric patients, requiring multiple daily dosing. The sustained-release tablet is large and hard to swallow; limiting its usefulness in this patient group.
Other studied uses	• Pulmonary Hypertension • Raynaud's Phenomenon • Preterm Labor • Nephropathy • Tourette's Syndrome		

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Adalat, Procardia, Adalat CC, Procardia XL, Nifedical XL (Nifedipine)**	**Cardene, Cardene SR, (Nicardipine)**	**DynaCirc, DynaCirc Cr, (Isradipine)**
Contraindications	**Contraindications** • Hypersensitivity to this or other calcium channel antagonists. **Precautions** • Angina (exacerbation) during initiation of treatment; with dosage increases; during beta-blocker withdrawal; taper slowly prior to calcium channel blocker therapy. • Aortic stenosis (reduced myocardial oxygenation with drug-induced hypotension) • Congestive heart failure (especially with combination beta-blocker therapy) • Gastrointestinal hypermotility (extended release dose forms) • Gastrointestinal obstruction (extended release dose forms) • Hypotension (with initial treatment; dose adjustments) • Impaired liver function (reduced metabolism, enhanced response). • Persistent dermatologic reactions induced by calcium antagonists have progressed to erythema multiforme or exfoliative dermatitis. Discontinue calcium antagonist treatment in this setting.		
Drug interactions	**Drug / Food Interactions:** Grapefruit juice may increase the serum concentrations of felodipine, nicardipine, nifedipine, nisoldipine, verapamil, and possibly amlodipine. **CYP450:** CYP3A4 has a major role in the metabolism of all the calcium channel blockers. Inducers and inhibitors of CYP3A4 can affect the metabolism of the dihydropyridines as well as verapamil and diltiazem. In general, diltiazem and verapamil inhibit other CYP3A4 substrates (eg, midazolam, carbamazepine), whereas the dihydropyridines do not.		
Major AEs / Warnings	▪ CHF has developed rarely, usually in patients receiving a beta-blocker, after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk, as the unloading effect would be of less benefit to these patients because of their fixed impedance to flow across the aortic valve. ▪ Decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time predominantly with verapamil, but may also be seen with diltiazem. ▪ Withdrawal syndrome: Abrupt withdrawal of calcium channel blockers may cause increased frequency and duration of chest pain; gradual taper of dose may be necessary. ▪ Increased angina ▪ Reflex tachycardia ▪ Hypotension		

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Adalat, Procardia, Adalat CC, Procardia XL, Nifedical XL (Nifedipine)**	**Cardene, Cardene SR, (Nicardipine)**	**DynaCirc, DynaCirc Cr, (Isradipine)**
Dosage adjustment in key populations	▪ Hepatic function impairment: The pharmacokinetics, bioavailability and patient response to verapamil and nifedipine may be significantly affected by hepatic cirrhosis. Since amlodipine, diltiazem, nicardipine, bepridil, felodipine and nimodipine are extensively metabolized by liver, use with caution in impaired hepatic function or reduced hepatic blood flow. ▪ Renal function impairment: Administer verapamil cautiously to patients with impaired renal function. Nifedipine – Plasma concentration is slightly increased in patients with renal impairment. Nicardipine - Mean plasma concentrations, AUC and maximum concentration were approximately twofold higher in patients with mild renal impairment. Doses must be adjusted. Use bepridil with caution in patients with serious renal disorders since the metabolites of bepridil are excreted primarily in the urine.		
Pipeline	See last page of Class Review		
Efficacy/ Summary	See last page of Class Review		

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Nimotop (Nimodipine)**	**Sular (Nisoldipine)**	**Norvasc (Amlodipine)**
Pharmacology	Dihydropyridine calcium channel blockers inhibit calcium ions from entering the “slow channels” or select voltage-senstivie areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina. Nifedipine and related dihydropyridines do not have significant direct effects on the atrioventricular conduction system or sinoatrial node at normal doses, and therefore do not have *direct* effects on conduction or automaticity.The dihydropyridines can cause reflex increases in heart rate because of their potent vasodilating effects. Vasodilatation of arterial resistance vessels causes a reflex increase in sympathetic response. Dihydropyridines have very modest negative inotropic effects. Any weak direct negative inotropic effect of the drug is overwhelmed by the strong reflex sympathetic response. The overall hemodynamic effect is a drop in blood pressure, an increase in heart rate and contractility, and an increase in cardiac output		
Generic available?	No	No	No
Date of FDA approval	Dec. 28, 1988	Feb. 2, 1995	July 31, 1992 (first patent expires 7/31/06, last patent expires 9/25/07); however on 3/20/2002 ***DRL filed an NDA for amlodipine maleate (different salt form of Pfizer's Norvasc®, amlodipine besylate) that was set to launch 8/03, but DRL has delayed launch to 12/2003 pending any further litigation.***
Manufacturer	Bayer	First Horizon	Pfizer
Dosage forms / route of admin.	▪ Nimotop Capsules, liquid: 30 mg	▪ Sular Tablets, extended release: 10, 20, 30, 40 mg	▪ Norvasc Tablets: 2.5, 5, 10 mg

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Nimotop (Nimodipine)**	**Sular (Nisoldipine)**	**Norvasc (Amlodipine)**
Dosing frequency	▪ Nimodipine: 60mg Q4hrs for 21 consecutive days	Sular: QD	Norvasc: QD
Generalized dosing guidelines	**SAH**: Commence therapy within 96 hours of the SAH, using 60 mg (two 30mg capsules) every 4hours for 21 consecutive days. **Hepatic function impairment:** Patients with hepatic cirrhosis have substantially reduced clearance and approximately doubled C_{max}. Reduce dosage to 30 mg every 4 hours with close monitoring of blood pressure and heart rate.	**HTN:** Administer orally once daily. Administration with a high-fat meal can lead to excessive peak drug concentration and should be avoided. Avoid grapefruit products before and after dosing. Initiate therapy with 20 mg orally once daily, then increase by 10 mg/week, as needed for BP. The usual maintenance dosage is 20 to 40 mg once daily. Doses beyond 60 mg once daily are not recommended. **Elderly/Hepatic function impairment:** Patients over 65 years of age or patients with impaired liver function are expected to develop higher plasma concentrations of nisoldipine. Monitor blood pressure closely during any dosage adjustment. A starting dose not exceeding 10mg daily is recommended in these patient groups.	**Hypertension:** Usual dose is 5 mg once daily. Maximum dose is 10 mg once daily. **Special populations**: Small, fragile, or elderly patients or patients with hepatic insufficiency may be started on 2.5 mg once daily; this dose also may be used when adding amlodipine to other antihypertensive therapy.. **Angina (chronic stable or vasospastic):** 5 to 10 mg, using the lower dose for elderly and patients with hepatic insufficiency. Most patients require 10 mg.
FDA labeled indications	• Subarachnoid hemorrhage (SAH)	• Hypertension	• Hypertension • Chronic stable angina • Vasospastic (Prinzmetal's or variant) angina

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Nimotop (Nimodipine)**	**Sular (Nisoldipine)**	**Norvasc (Amlodipine)**
Pediatric labeling	Not FDA approved for use in pediatrics	Not FDA approved for use in pediatrics	Not FDA approved in pediatrics; however pediatric patients seem to require a higher dose of amlodipine on a mg/ kg basis than adults, and appear to require a twice-daily dosing regimen to retain blood pressure control
Other studied uses	HTN Cerebral Ischemia without stroke Cluster headache Depression Hiccups Migraine	• Pulmonary Hypertension • Raynaud's Phenomenon • Preterm Labor • Nephropathy • Tourette's Syndrome	
Contraindications	**Contraindications** • Hypersensitivity to this or other calcium channel antagonists. **Precautions** • Angina (exacerbation) during initiation of treatment; with dosage increases; during beta-blocker withdrawal; taper slowly prior to calcium channel blocker therapy. • Aortic stenosis (reduced myocardial oxygenation with drug-induced hypotension) • Congestive heart failure (especially with combination beta-blocker therapy) • Gastrointestinal hypermotility (extended release dose forms) • Gastrointestinal obstruction (extended release dose forms) • Hypotension (with initial treatment; dose adjustments) • Impaired liver function (reduced metabolism, enhanced response). • Persistent dermatologic reactions induced by calcium antagonists have progressed to erythema multiforme or exfoliative dermatitis. Discontinue calcium antagonist treatment in this setting.		
Drug interactions	**Drug / Food Interactions:** Grapefruit juice may increase the serum concentrations of felodipine, nicardipine, nifedipine, nisoldipine, verapamil, and possibly amlodipine. **CYP450:** CYP3A4 has a major role in the metabolism of all the calcium channel blockers. Inducers and inhibitors of CYP3A4 can affect the metabolism of the dihydropyridines as well as verapamil and diltiazem. In general, diltiazem and verapamil inhibit other CYP3A4 substrates (eg, midazolam, carbamazepine), whereas the dihydropyridines do not.		

Dihydropyridine Calcium Channel Blockers (DHPCCB)			
Characteristic	**Nimotop (Nimodipine)**	**Sular (Nisoldipine)**	**Norvasc (Amlodipine)**
Major AEs / Warnings	▪ CHF has developed rarely, usually in patients receiving a -blocker, after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk, as the unloading effect would be of less benefit to these patients because of their fixed impedance to flow across the aortic valve. ▪ Decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in so Withdrawal syndrome: ▪ Abrupt withdrawal of calcium channel blockers may cause increased frequency and duration of chest pain.; gradual taper of dose may be necessary. ▪ Increased angina ▪ Reflex tachycardia ▪ Hypotension		
Dosage adjustment in key populations	▪ Hepatic function impairment: The pharmacokinetics, bioavailability and patient response to verapamil and nifedipine may be significantly affected by hepatic cirrhosis. Since amlodipine, diltiazem, nicardipine, bepridil, felodipine and nimodipine are extensively metabolized by liver, use with caution in impaired hepatic function or reduced hepatic blood flow. ▪ Renal function impairment: Administer verapamil cautiously to patients with impaired renal function. Nifedipine - Plasma concentration is slightly increased in patients with renal impairment. Nicardipine - Mean plasma concentrations, AUC and maximum concentration were approximately twofold higher in patients with mild renal impairment. Doses must be adjusted. Use bepridil with caution in patients with serious renal disorders since the metabolites of bepridil are excreted primarily in the urine.		
Pipeline	See Last page of Class Review		
Summary/Efficacy	See Last page of Class Review		

Dihydropyridine Calcium Channel Blockers (DHPCCB)	
Characteristic	**Plendil (Felodipine)**
Pharmacology	Dihydropyridine calcium channel blockers inhibit calcium ions from entering the "slow channels" or select voltage-senstivie areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina. Nifedipine and related dihydropyridines do not have significant direct effects on the atrioventricular conduction system or sinoatrial node at normal doses, and therefore do not have *direct* effects on conduction or automaticity.The dihydropyridines can cause reflex increases in heart rate because of their potent vasodilating effects. Vasodilatation of arterial resistance vessels causes a reflex increase in sympathetic response. Dihydropyridines have very modest negative inotropic effects. Any weak direct negative inotropic effect of the drug is overwhelmed by the strong reflex sympathetic response. The overall hemodynamic effect is a drop in blood pressure, an increase in heart rate and contractility, and an increase in cardiac output
Generic available?	No
Date of FDA approval	July 25, 1991
Manufacturer	▪ AstraZeneca
Dosage forms / route of admin.	▪ Plendil Tablets, extended release: 2.5, 5,10 mg
Dosing frequency	QD
Generalized dosing guidelines	**HTN**: Starting dose is 5 mg once daily, the dosage can be decreased to 2.5 mg or increased to 10 mg once daily. The recommended dosage range is 2.5 to 10 mg once daily. ▪ In clinical trials, doses above 10 mg daily increased blood pressure (BP) response; however this dosage also caused a large increase in the rate of peripheral edema and other vasodilatory adverse events. ▪ Modification of the recommended dosage usually is not required in renal impairment. ▪ Take without food or with a light meal. Swallow whole; do not crush or chew.
Dosages in special populations	**Elderly:** Patients over 65 years are likely to develop higher plasma felodipine concentrations. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (2.5 mg daily). Closely monitor BP during dosage adjustment. **Liver function impairment:** Patients with impaired liver function may have elevated plasma drug concentrations and may respond to lower doses; closely monitor BP during dosage adjustment of felodipine.
FDA labeled indications	Hypertension

Dihydropyridine Calcium Channel Blockers (DHPCCB)	
Characteristic	**Plendil (Felodipine)**
Pediatric labeling	Not FDA approved for use in pediatric patients. Some generalized guidelines for children exist - Initial dose, 0.1 mg/kg per day in one or two doses - Usual dose, 0.1 to 0.6 mg/kg per day in one or two doses -Maximum dose, 0.6 mg/kg per day up to 20 mg per day Tablet must be swallowed whole and is relatively large in size for infants and young children
Other studied uses	• Pulmonary Hypertension • Raynaud's Phenomenon • Preterm Labor • Nephropathy • Tourette's Syndrome

Dihydropyridine Calcium Channel Blockers (DHPCCB)	
Characteristic	**Plendil (Felodipine)**
Contraindications	**Contraindications** • Hypersensitivity to this or other calcium channel antagonists. **Precautions** • Angina (exacerbation) during initiation of treatment; with dosage increases; during beta-blocker withdrawal; taper slowly prior to calcium channel blocker therapy. • Aortic stenosis (reduced myocardial oxygenation with drug-induced hypotension) • Congestive heart failure (especially with combination beta-blocker therapy) • Gastrointestinal hypermotility (extended release dose forms) • Gastrointestinal obstruction (extended release dose forms) • Hypotension (with initial treatment; dose adjustments) • Impaired liver function (reduced metabolism, enhanced response). • Persistent dermatologic reactions induced by calcium antagonists have progressed to erythema multiforme or exfoliative dermatitis. Discontinue calcium antagonist treatment in this setting.
Major AEs / Warnings	▪ CHF has developed rarely, usually in patients receiving a -blocker, after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk, as the unloading effect would be of less benefit to these patients because of their fixed impedance to flow across the aortic valve. ▪ Decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in so Withdrawal syndrome: ▪ Abrupt withdrawal of calcium channel blockers may cause increased frequency and duration of chest pain.; gradual taper of dose may be necessary. ▪ Increased angina ▪ Reflex tachycardia ▪ Hypotension
Drug interactions	**Drug / Food Interactions:** Grapefruit juice may increase the serum concentrations of felodipine, nicardipine, nifedipine, nisoldipine, verapamil, and possibly amlodipine. **CYP450:** CYP3A4 has a major role in the metabolism of all the calcium channel blockers. Inducers and inhibitors of CYP3A4 can affect the metabolism of the dihydropyridines as well as verapamil and diltiazem. In general, diltiazem and verapamil inhibit other CYP3A4 substrates (eg, midazolam, carbamazepine), whereas the dihydropyridines do not.

Dihydropyridine Calcium Channel Blockers (DHPCCB) Summary	
Pipeline Agents/Future Products	▪ Lercanidipine (Forrest Pharmaceuticals, not yet FDA approved). December 2002, FDA requested more clinical data prior to approval; however, the drug is currently marketed in Great Britain and other European countries. Lercanidipine is considered a third generation dihydropyridine calcium channel blocker that has high lipophilicity (which gives it a long half-life and ability for once daily dosing). Lercanidipine selectively inhibits the influx of extracellular calcium through voltage-gated calcium channels, but not through receptor – operated calcium channels. ▪ Lacidipine (An NDA was filed in 1989 by Glaxo and is approved in Great Britain but not the US.) also a third generation dihydropyridine similar in kinetics to Lercanidipine
Unique Features/Advantages Summary/Efficacy	▪ The Advisory Council to Improve Outcomes Nationwide in Heart Failure (ACTION-HF) indicated that two long-acting DHP-CCBs [felodipine (Plendil®) amd amlodipine (Norvasc®)] may be used with relative safety in patients with chronic heart failure. Two major clinical trials: PRAISE (amlodipine) and V-HeFT III (felodipine) supported that both felodipine and amlodipine have no beneficial effects, but have no detrimental effects in patients with heart failure who need greater treatment for blood pressure or angina that does not respond to standard agents. ▪ Short-acting DHP-CCBs have been show to increase sympathomimetic activity that enhances the already elevated sympathetic activity in patients with heart failure. This increase in neurohormonal systems, notably the sympathetic and renin-angiotensin systems, induces deleterious changes in the myocardial tissue, thus worsening the clinical condition of heart failure. ▪ In administering immediate-release nicardipine and nifedipine, the relatively large peak to trough differences in blood pressure (BP) effect has yielded these agents of limited clinical utility. ▪ PRAISE-II was designed to replicate PRAISE-I in a sub-set of patients with non-ischemic idiopathic dilated cardiomyopathy who exhibited a non-significant trend in PRAISE –I towards decreased mortality. PRAISE II however ***was not*** able to replicate trends seen in PRAISE –I. There was no difference in all-cause or cardiac mortality and cardiac mortality and cardiac event rates between amlodipine and placebo, with trends in favor of the placebo group. The dangers of making inferences from non-significant trends from clinical trials has been noted. ▪ Norvasc differs from nifedipine and other currently marketed dihydropyridines by virtue of its high oral bioavailability (F=65%) and long elimination half-life (35 to 50 hours) enabling once daily dosing without altering the dosage formulation. Norvasc is the only once daily formulation that may be crushed for patients with swallowing difficulties. Lercanidipine (NDA filed 12/02; and Lacidipine (availabe in Europe) have high lipophilicity that also allow for once daily dosing. ▪ In animals, nimodipine had a greater effect on cerebral arteries than on other arteries, possibly because it is highly lipophilic. While studies show a favorable effect on severity of neurological deficits caused by cerebral vasospasm following SAH, there is no arteriographic evidence that the drug prevents or relieves spasm of these arteries. Therefore, the actual mechanism of action is unknown and it is the only CCB indicated for use in SAH.

Efficacy and safety of calcium channel blockers in heart failure: focus on recent trials with second-generation dihydropyridines.

de Vries RJ, van Veldhuisen DJ, Dunselman PH.
Am Heart J. 2000 Feb;139(2 Pt 1):185-94.

Department of Cardiology/Thoraxcenter, University Hospital Groningen, and the Department of Cardiology, Ignatius Hospita, Breda.

BACKGROUND: Chronic heart failure (CHF) has high morbidity and mortality rates despite treatment with angiotensin-converting enzyme inhibitors, diuretics, and digoxin. Adjunctive vasodilation through calcium channel blockade has been suggested as potentially useful. However, the first-generation calcium channel blockers, including the dihydropyridine nifedipine, showed disappointing results in CHF. The second-generation dihydropyridines were expected to be of more value, and of all the calcium channel blockers, these drugs were the ones most studied in patients with CHF. METHODS AND RESULTS: The Medline databank was used to search studies in human beings (published in 1990 or later) that used dihydropyridines in patients with CHF. The references of the studies found were subsequently checked for additional data. In 17 studies and more than 2000 patients with CHF, no consistent beneficial effect was observed with regard to exercise tolerance and functional capacity, whereas plasma neurohormones were not affected. On the other hand, in general, no worsening of CHF was seen with these second-generation dihydropyridines. Two larger studies (PRAISE and V-HeFT III) have given some estimates on the long-term effects of dihydropyridines, and no overall influence on mortality rate was found. Of note, subanalysis of the PRAISE study has suggested that in patients with a nonischemic cause of CHF, amlodipine might have a beneficial effect on survival[*]. CONCLUSIONS: In this review we have focused on the efficacy and safety of dihydropyridines in patients with CHF, as reported in recent trials. The data do not support the use of dihydropyridines when primarily given as treatment for CHF. The results, however, suggest that these drugs can be safely given to patients with left ventricular dysfunction or CHF who need additional treatment for angina pectoris or hypertension.

[*] Note this was not proven in PRAISE II. PRAISE-II was designed to replicate PRAISE-I in a sub-set of patients with non-ischemic idiopathic dilated cardiomyopathy who exhibited a non-significant trend in PRAISE –I towards decreased mortality.

Comparison of the efficacy of dihydropyridine calcium channel blockers in African American patients with hypertension. ISHIB Investigators Group. International Society on Hypertension in Blacks. (CAB Trial)

Hall WD, Reed JW, Flack JM, Yunis C, Preisser J.

Arch Intern Med. 1998 Oct 12;158(18):2029-34.
Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA.

BACKGROUND: Hypertension is a prevalent disease among African Americans, and successful treatment rates are low. Since calcium channel blockers are well-tolerated and efficacious in African Americans, we undertook this study to compare the efficacy, safety, and tolerability of 3 commonly prescribed calcium channel blockers: amlodipine besylate (Norvasc), nifedipine coat core (CC) (Adalat CC), and nifedipine gastrointestinal therapeutic system (GITS) (Procardia XL). METHODS: One hundred ninety-two hypertensive patients across 10 study centers were randomly assigned to double-blind monotherapy with amlodipine besylate (5 mg/d), nifedipine CC (30 mg/d), or nifedipine GITS (30 mg/d) for 8 weeks. Patients not achieving therapeutic response after 4 weeks had their dose doubled for the next 4 weeks. The primary end point was a comparison of the average reduction (week 8 minus baseline) in 24-hour ambulatory diastolic blood pressure (DBP). Secondary end points included a comparison of average 24-hour ambulatory systolic blood pressure (SBP), office SBP or DBP reduction, responder rates, safety, and tolerability. RESULTS: One hundred sixty-three patients were evaluable for efficacy after 8 weeks. There was no significant difference in the average 24-hour ambulatory DBP (-8.5, -9.0, and -6.1 mm Hg, respectively) or SBP (-14.3, -15.7, and -11.8 mm Hg, respectively) reduction. Average office SBP and DBP were reduced to a comparable degree (19-22 mm Hg [P =.50] and 12-14 mm Hg [P =.51], respectively). Responder rates (DBP <90 or reduced by > or = 10 mm Hg) were similar (P = .38). Discontinuation rates and adverse event frequency were distributed similarly across the 3 treatment groups. CONCLUSION: The efficacy, safety, and tolerability of the 3 dihydropyridine calcium channel blockers are equivalent in African Americans with stages 1 and 2 hypertension.

Calcium channel blockers in hypertension: reappraisal after new trials and major meta-analyses.

Opie LH.

Am J Hypertens. 2001 Oct;14(10):1074-81
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This review evaluates the current position of calcium channel blockers (CCB) in antihypertensive treatment in the light of three major comparative studies and two extensive meta-analyses. The latter both show that CCB are equivalent to conventional (initial beta-blocker or diuretic therapy) when total and cardiovascular mortality are the end points. Divergent points between the meta-analyses include stroke and myocardial infarction (MI). One meta-analysis compared CCB with conventional therapy, to find a small 13% reduction in stroke and a small, nonsignificant 12% increase in MI. The other meta-analysis found a 26% increase in MI when CCB were compared with all other therapies including the angiotensin converting enzyme (ACE) inhibitors. This increase was most robust ($P < .001$) when comparing CCB with ACE inhibitors, consonant with proposed protective effects of ACE inhibitors on cardiovascular risk. At present, only the comparison of CCB with conventional therapy, and not that with ACE inhibitors, rests on secure comparative data. When cost is compelling, conventional therapy is less expensive. For the individual patient, issues of quality of life (for example, impotence with diuretics and beta-blockers) might be decisive. Nonetheless, beta-blockers are preferred in postinfarct patients or in those with heart failure or unstable angina (a contraindication to dihydropyridines in the absence of beta-blockade). In others, the benefits of only a borderline stroke reduction with CCB versus an equally borderline increase in MI should be evaluated for each individual patient, taking into account the age group and the patient's preferences. In conclusion, overall CCB are neither better nor worse than conventional therapy, allowing for possible small differences in stroke and MI. The ACE inhibitors may protect better, although data are incomplete.

Calcium antagonists in hypertension: from hemodynamics to outcomes.

Messerli FH.
Am J Hypertens. 2002 Jul;15(7 Pt 2):94S-97S.

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Hypertension, by definition, is a hemodynamic disorder. A high cardiac output and a normal systemic vascular resistance characterize the young hypertensive patient. As hypertension progresses, resistance becomes progressively elevated and cardiac output returns to normal. The elderly patient with hypertension has very high systemic vascular resistance and low cardiac output. Antihypertensive drugs should not only lower arterial pressure but also bring other hemodynamic parameters as well as functional and structural changes of the cardiovascular system back to normal. With the notable exception of the classic beta-blockers, all antihypertensive drug classes, including the vasodilating beta-blockers, increase or maintain cardiac output and lower systemic vascular resistance. Calcium antagonists, although a very heterogeneous group, have been shown to have a similar effect on systemic hemodynamics. Initially, the short-acting agents (even verapamil) produce a reflex increase in heart rate and cardiac output with a decrease in systemic vascular resistance. This reflexive cardiac acceleration is not seen with the extended-release or longer-acting formulations, which usually maintain cardiac output and decrease systemic resistance. Lercanidipine is a novel calcium antagonist that has been shown to differ from other dihydropyridines in that the incidence of vasodilatory edema for any given decrease in blood pressure is less pronounced. Whereas all dihydropyridine calcium antagonists dilate the afferent arteriole in the kidney, preclinical studies have shown that lercanidipine also produces dilation of the efferent vessel. Similar balanced pre- and postcapillary vasodilation may be an explanation for the lower incidence of vasodilatory edema seen clinically with lercanidipine. These micro- and macrovascular features make lercanidipine an attractive new member in the arsenal of the powerful dihydropyridine calcium antagonists.

Effects of long-acting calcium channel antagonists on neurohumoral factors: comparison of nifedipine coat-core with amlodipine.

Tsutamoto T, Tsutsui T, Maeda K, Hayashi M, Wada A, Ohnishi M, Fujii M, Ishii C.
J Cardiovasc Pharmacol. 2003 Jan;41 Suppl 1:S77-81

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Calcium channel antagonists can induce sympathetic hyperactivity, leading to a poor prognosis for hypertensive patients. Nifedipine formulations that allow once-daily administration are now available for use in clinical practice. To compare the effects of nifedipine with those of amlodipine, we studied 36 essential hypertensive patients. Those who had been administered nifedipine sustained-release were treated with amlodipine in place of nifedipine sustained-release, and those who had been administered amlodipine were treated with nifedipine coat-core in place of amlodipine. Substitution of nifedipine sustained-release by amlodipine had no significant effect on hypertensive symptoms. However, the plasma levels of norepinephrine, renin, and aldosterone were significantly lower ($p < 0.001$-0.05) in patients taking amlodipine in place of nifedipine sustained-release. Substitution of amlodipine by nifedipine coat-core again had no significant effect on hypertensive symptoms. However, the plasma levels of norepinephrine, renin, and aldosterone did not change significantly after the substitution. These findings indicate that, at the effective anti-hypertensive concentrations of nifedipine coat-core and amlodipine, nifedipine coat-core may not increase sympathetic nerve activity as is observed with amlodipine. The results also suggest that the duration of action of nifedipine formulations is an important determinant for nifedipine-induced hyperactivity in the reflex sympathetic nerve and the renin-angiotensin systems.

An updated meta-analysis of calcium-channel blockers in the prevention of restenosis after coronary angioplasty.

Dens J, Desmet W, Piessens J.
Am Heart J. 2003 Mar;145(3):404-8.

Department of Cardiology, University Hospital Gasthuisberg, Leuven, Belgium.

BACKGROUND: In 1994, a meta-analysis of 5 small randomized trials reported a 30% reduction in the odds of angiographic restenosis when calcium-channel blockers (CCB) were given after percutaneous coronary intervention. Recently, the results of 2 large similar trials (Nisoldipine In Coronary Artery Disease in Leuven [NICOLE], and Coronary AngioPlasty Amlodipine in REstenosis Study [CAPARES]) were published. An extended meta-analysis including the results of the latter trials was performed. METHODS: A total of 2380 patients were analyzed. Statistical analysis included calculation of odds ratios for each trial, common odds ratio, and homogeneity for treatment effects across trials. RESULTS: The incidence of angiographic restenosis was 36% in the CCB-treated group and 42% in the placebo group. The odds ratio of restenosis with CCB therapy was 0.78 (95% CI 0.64-0.95) compared with control patients (P =.01). Treatment effects were homogeneous across the trials. For the combined end point of death, coronary artery bypass grafting, repeat percutaneous transluminal coronary angioplasty, and myocardial infarction, 126 of 626 events occurred in the CCB group and 191 of 655 in the placebo group (odds ratio 0.61 [95% CI 0.47-0.80], P <.001). CONCLUSIONS: This extended meta-analysis confirmed a reduction in the odds of restenosis and clinical events when CCBs were added to standard therapy after percutaneous coronary intervention.

Emerging data on calcium-channel blockers: the COHORT study.

Zanchetti A.
Clin Cardiol. 2003 Feb;26(2 Suppl 2):II17-20.

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Multiple studies have demonstrated dihydropyridine calcium-channel blocker (CCB) therapy to be appropriate for the treatment of hypertension, as is reflected in treatment guidelines such as the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in the United States and the 1999 World Health Organization-International Society of Hypertension report. As with any drug class, successful treatment with CCBs depends on good patient compliance, which often hinges on drug tolerability. The differing characteristics among the various generations of CCBs may contribute to some compounds demonstrating superior tolerability. To test this hypothesis, the COHORT trial (named for the large group of participants) was undertaken in 828 elderly hypertensive patients aged > or = 60 years. This trial investigated the possible differences in patient tolerability between the third-generation agent amlodipine and the latest-generation agents lercanidipine and lacidipine. The primary endpoint of the study was the percentage of patients reporting edema, the most common side effect associated with CCB therapy. The study results indicated that while all three treatments were similarly efficacious in lowering blood pressure, lercanidipine and lacidipine were much better tolerated than amlodipine whether they were used as single agents or as initial therapy combined with other antihypertensive drugs. These newest-generation dihydropyridine CCBs offer the potential to reduce side effects, improve patient compliance, and ultimately help patients reach target blood pressures as recommended by the aforementioned guidelines.

Comparison of effects of nisoldipine-extended release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris.

Pepine CJ, Cooper-DeHoff RM, Weiss RJ, Koren M, Bittar N, Thadani U, Minkwitz MC, Michelson EL, Hutchinson HG; Comparative Efficacy and Safety of Nisoldipine and Amlodipine (CESNA-II) Study Investigators.
Am J Cardiol. 2003 Feb 1;91(3):274-9.

Partially funded by Aztra-Zeneca (makers of Plendil® – not studied in this trial)

University of Florida College of Medicine, Gainesville, Florida 32610, USA.

The efficacy and safety of nisoldipine-extended release (ER) and amlodipine were compared in a 6-week multicenter, randomized, double-blind, double-dummy, parallel group, titration-to-effect trial in patients with stage 1 to 2 systemic hypertension (90 to 109 mm Hg diastolic blood pressure [BP]) and chronic stable angina pectoris. After a 3-week placebo run-in period, patients (n = 120) were randomly assigned to active treatment with either nisoldipine-ER (20 to 40 mg) or amlodipine (5 to 10 mg) once daily, titrated as necessary after 2 weeks to achieve diastolic BP <90 mm Hg. After 6 weeks, the mean reduction in systolic/diastolic BP from baseline was 15/13 mm Hg with nisoldipine-ER and 13/11 mm Hg with amlodipine (p = NS/p = NS). Both drugs resulted in similar BP responder rates (diastolic BP <90 mm Hg in 87% of patients who received nisoldipine-ER and 78% of patients on amlodipine, p = NS) and anti-ischemic responder rates (increasing exercise time >20% in 20% and 27%, respectively [p = NS], and increasing exercise time >60 seconds in 32% and 29% of patients, respectively [p = NS]. Also, after 6 weeks of active therapy, there was a similar mean increase in total exercise duration (23 seconds in the nisoldipine-ER group and 21 seconds in the amlodipine group, p = NS). Neither drug increased heart rate and both decreased frequency of anginal episodes. Adverse events were infrequent, and typically were vasodilator-related effects (including headache and peripheral edema) that occurred with somewhat higher incidence in the nisoldipine-ER group. Thus, nisoldipine-ER and amlodipine provided comparable antihypertensive and anti-ischemic efficacy, and both were generally well tolerated.

Shanghai trial of nifedipine in the elderly (STONE).

Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Page V, Ghadirian P, LeLorier J, Hamet P.

J Hypertens. 1996 Oct;14(10):1237-45.
Shanghai Institute of Hypertension, Rui Jun Hospital of Shanghai, Shanghai Second Medical University, People's Republic of China.

OBJECTIVE: To assess the effectiveness of nifedipine treatment in elderly hypertensives. METHODS: A single-blind trial was conducted under the direction of the Shanghai Institute of Hypertension in 1632 subjects aged 60-79 years alternatively allocated to either nifedipine or placebo after a 4-week placebo run-in period between 1987 and 1990 with mean follow-up of 30 months. Clinical events and risk modification were analysed in collaboration with the University of Montreal. Seventy-four patients with severe hypertension were reallocated to active nifedipine treatment after placebo run-in. RESULTS: Cox's proportional hazards model accounting for covariates demonstrated a highly significant decrease in the probability of events: 'original treatment assignment' analysis indicated that 77 events occurred in the placebo and 32 in the nifedipine group. Similar significances were achieved with 'actual treatment' or 'changes excluded' (excluding reallocated subjects) analyses. A significant reduction in relative risk was observed for strokes and severe arrhythmia with an overall decrease from 1.0 to 0.41 (95% confidence interval 0.27-0.61). CONCLUSION: Nifedipine treatment diminished the number of severe clinical outcomes in elderly hypertensives significantly.

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine Fast influx channel block Vascor (Bepridil)**	**Benzothiazepine Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA Branded generics: Cartia XT, Diltia XT (Diltiazem)**
Pharmacology	Bepridil possesses characteristics of the traditional calcium antagonists, inhibiting calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization and producing a relaxation of coronary vascukar smooth muscle and coronary vasodilation. However, bepridil may also inhibit fast sodium channels (inward) which may account for some if its side effects (eg arrhytmias); bepridil may also have a direct bradycardia effect via direct action on the SA node.	Diltiazem, a benzothiazepine derivative, is a calcium antagonist which interferes with the influx of extracellular calcium through "slow" channels located in the cell membrane of cardiac smooth muscle. At slightly higher doses than those used clinically, Diltiazem also inhibits the influx of sodium through "fast" channels. Diltiazem also speeds the exit of calcium from the cell by stimulating adenosine triphosphate-dependent calcium pumps and sodium-potassium pumps. Diltiazem’s calcium channel inhibition in cardiac pacemaker cells results in decreased sinus node automaticity and decreased atrioventricular (AV) node conductivity. Calcium channel inhibition in smooth muscle cells results in arterial vasodilation. Vasodilation due to diltiazem is preferentially in the coronary vasculature. Hemodynamic effects of diltiazem include a dose-related reduction in myocardial oxygen consumption, cardiac work, blood pressure, and heart rate. Diltiazem inhibits platelet aggregation in vitro. The clinical significance of this in unknown. The calcium antagonists, DHPCCB (nifedipine-like) and NDHPCC (diltiazem/verapamil) have differing pharmacologic properties and therefore are used for different clinical conditions. Diltiazem and verapamil produce equivalent slowing of atrioventricular (AV) nodal conduction, but verapamil prolongs the AV nodal refractoriness to a greater degree. Nifedipine increases AV nodal conduction and shortens AV nodal refractoriness. verapamil and diltiazem are useful for treating and preventing supraventricular arrhythmias. Diltiazem possesses less negative ionotropic activity than Verapamil and only one-tenth the vasodilator potency of nifedipine.
Manufacturer	OrthoMcNeil	Cardizem LA (Biovail) All others are available generically
Date of FDA Approval	December 28, 1990	Cardizem LA : February 6, 2003
Generic available?	No	▪ Cardizem LA: not available generically Yes (diltiazem IR tablets diltiazem SR-sustained release capsules, diltiazem extended release capsules, CD and XR, Tiazac has a newly approved generic (Taztia XT)

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine Fast influx channel block Vascor (Bepridil)**	**Benzothiazepine Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA Branded generics: Cartia XT, Diltia XT (Diltiazem)**
Dosage forms / route of admin.	▪ Vascor Tablets: 200, 300, 400 mg	▪ Cardizem Tablets: 30, 60, 90, 120 mg ▪ Cardizem SR Capsules, sustained release: 60, 90, 120 mg ▪ Cardizem CD, Dilacor XR, Tiazac Capsules, sustained release: 120, 180, 240mg ▪ Cardizem CD, Tiazac Capsules, sustained release: 300 mg ▪ Cartia XT, Diltia XT Capsules, extended release: 120, 180, 240mg ▪ Cartia XT Capsules, extended release: 300mg ▪ Tiazac, Cardizem CD Capsules, extended release: 360 mg ▪ Tiazac Capsules, extended release: 420 mg ▪ Cardizem LA Tablets, extended release: 120, 180, 240, 300, 360, 420 mg ▪ Diltiazem IV 5mg/ml, In 5, 10, and 25 mL vials.
Dosing frequency	Bepridil: QD	Immediate Release ▪ IR Tablets: TID or QID Sustained release ▪ Cardizem SR: BID ▪ Cardizem CD: QD ▪ Dilacor XR: QD ▪ Tiazac: QD ▪ Cartia XT: QD ▪ Diltia XT: QD ▪ Cardizem LA: QD

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine Fast influx channel block Vascor (Bepridil)**	**Benzothiazepine Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA Branded generics: Cartia XT, Diltia XT (Diltiazem)**
General Dosing Guidelines	(Adults) Usual starting dose 200mg once daily. Adjust upward after 10 days. Max 400mg/day; minimum effective daily dose 200mg.	Cardizem Immediate Release: (Adults) Starting dose 30mg 4 times daily before meals and at bedtime. Increase dosage gradually at 1- to 2-day intervals until optimum response reached. Usual optimum range 180 to 360mg/day. Cardizem SR: (Adults) Start with 60 to 120mg twice daily, then individualize dosage. Usual optimum range 240 to 360mg/day. (Children) Not recommended. Cardizem CD and Cartia XT: (Adults) Hypertension: When used alone, usual starting dose 180 to 240mg once daily. Titrate to individual need. Max effect usually seen within 14 days of chronic therapy. Usually 240 to 360mg once daily. Angina: Initially 120 or 180mg/day. Individualize. Max 480mg/day. (Children) Not recommended. Dilacor XR and Diltia XT: Take in morning on empty stomach. (Adults) Individualize. Initially 180 or 240mg once daily. Range 180 to 480mg/day. May increase to 540mg/day. Tiazac and Taztia XT : Hypertension: Initially 120 to 240mg once daily. Adjust at 2-week intervals. Max 540mg/day. Chronic stable angina: Initially 120 to 180mg once daily. Adjust at 7- to 14-day intervals. Cardizem LA : For the treatment of hypertension, the recommended starting dose is 180 to 240mg/day. Doses may be titrated to 360mg, and up to a maximum of 540mg daily as needed to achieve BP goals; may be taken in the morning or evening
Pediatric Labeling	None	None
FDA Labeled Indications	▪ Chronic stable angina (bepridil)	▪ Angina pectoris due to coronary artery spasm ▪ Chronic stable angina (classic effort-associated angina) ▪ Essential hypertension (sustained release only)

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine Fast influx channel block Vascor (Bepridil)**	**Benzothiazepine Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA Branded generics: Cartia XT, Diltia XT (Diltiazem)**
Other studied uses	▪ Supraventricular arrythmias (SVT) ▪ Ventricular arrythmias	▪ Pulmonary hypertension ▪ Raynaud's phenomenon ▪ Diabetic nephropathy ▪ Hypertropic cardiomyopathy (diastolic dysfunction) ▪ Nocturnal leg cramps ▪ Migraine prophylaxis ▪ Afib/Aflutter ▪ Paroxysmal supraventricular arrythmias (PSVTs) ▪ Ventricular arrythmias ▪ Myocardial infarction: 1. Diltiazem has neutral to slight benefit on overall mortality (non Q-wave patient subset) 2. Reinfarction rate reduced significantly with diltiazem in subsets with existing hypertension but without CHF following first MI 3. Revascularization procedure rate (PTCA/CABG) reduced significantly with diltiazem following thrombolytic use following first MI
Contraindications	▪ Hypersensitivity to the drug in question ▪ Sick sinus syndrome (bepridil, diltiazem, verapamil) ▪ 2nd or 3rd degree heart block – except with functioning pacemaker (bepridil, diltiazem, verapamil) ▪ Hypotension < 90 mm Hg systolic (bepridil, diltiazem, verapamil) ▪ Acute MI and pulmonary congestion (diltiazem) ▪ Severe left ventricular dysfunction, cardiogenic shock, severe CHF unless related to SVT treatable with verapamil, ▪ C/I in patients with atrial flutter or atrial fibrillation and an accessory bypass tract (Wolff-Parkinson-White,WPW). (verapamil and diltiazem) ▪ History of serious ventricular dysrhythmias, uncompensated cardiac insufficiency, congenital QT interval prolongation, combination with other drugs that increase QT interval (bepridil)	
Drug interactions	Cyclosporine, Prograf® (Tacrolimus) and Rapamune® (Sirolimus) levels increase with concurrent use of diltiazem and verapamil (this interaction has been used clinically to more effectively treat patients) Digitalis glycosides levels may increase by 50% with concurrent verapamil administration Beta Blockers may decrease AV node conduction and induce bradycardia with concurrent administration	

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine** **Fast influx channel block** **Vascor** **(Bepridil)**	**Benzothiazepine** **Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA** **Branded generics: Cartia XT, Diltia XT** **(Diltiazem)**
Major AEs / Warnings	Major AEs: Most common: Upper-GI distress, constipation, diarrhea, dizziness, asthenia, nervousness, edema, headache, dizziness, asthenia, bradycardia, flushing, rash, nausea, constipation, anorexia. Most serious: Torsades de pointes arrhythmia, prolonged QT interval, bradycardia, 1st-degree heart block. Warnings: ▪ Pregnancy: Category C, Induction of new serious arrhythmias (bepridil), Hypotension, Congestive heart failure, Cardiac conduction, Premature ventricular contractions (PVCs), Antiplatelet effects, Withdrawal syndrome, Agranulocytosis, Hepatic/ Renal function impairment, Increased angina, Increased intracranial pressure, Acute hepatic injury, Edema	
Dosage adjustment in key populations	▪ Hepatic function impairment: The pharmacokinetics, bioavailability and patient response to verapamil and nifedipine may be significantly affected by hepatic cirrhosis. Since amlodipine, diltiazem, nicardipine, bepridil, felodipine and nimodipine are extensively metabolized by liver, use with caution in impaired hepatic function or reduced hepatic blood flow. ▪ Renal function impairment: Administer verapamil cautiously to patients with impaired renal function. Use bepridil with caution in patients with serious renal disorders since the metabolites of bepridil are excreted primarily in the urine.	

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine Fast influx channel block Vascor (Bepridil)**	**Benzothiazepine Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA Branded generics: Cartia XT, Diltia XT (Diltiazem)**
Pipeline Agents	▪ T-channel blockers: The plasma membrane calcium channels, which include the L- and T-type channels, are of clinical interest for pharmacologic therapy. T-type calcium channels, which activate contraction in vascular smooth muscle but have little or no role in cardiac excitation-contraction coupling, appear to be involved in signal transduction pathways that promote cell growth and proliferation. Calcium channel blockers that selectively block T-type calcium channels, therefore, offer a novel approach to cardiovascular drug therapy. 1. DP-3005 made by Diakron is the pro-type T-channel blocker in development. Note: Posicor® (mibefradil) was a combined L and T- channel blocker that was withdrawn from the market in June of 1998.	

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)		
Characteristic	**Non-dihydropyridine** **Fast influx channel block** **Vascor** **(Bepridil)**	**Benzothiazepine** **Cardizem, Cardizem CD, Cardizem SR, Tiazac, Dilacor , Cardizem LA** **Branded generics: Cartia XT, Diltia XT** **(Diltiazem)**
Unique Features/ Advantages	• Bepridil is only indicated for chronic stable angina in patients that have failed or are intolerant to other anti-anginal therapy. • Bepridil is a non-selective calcium channel blocker. It will also affect sodium and potassium channels; due to its pro-arrhythmic effects (risk of torsades de pointes) and association with cases of agranulocytosis, it should be reserved for patients who have failed (or are intolerant to) other antianginals.	• Diltiazem was as effective as treatment based on diuretics, beta-blockers, or both in preventing the combined primary endpoint of all stroke, myocardial infarction, and other cardiovascular death (Nordil trial). • Diltiazem and Verapamil are the only subset of CCBs that delay AV conduction or cause sinus node depression in doses used clinically ▪ Diltiazem has been shown the following in patients with myocardial infarction: 1. Diltiazem has neutral to slight benefit on overall mortality (non Q-wave patient subset) 2. Reinfarction rate reduced significantly with diltiazem in subsets with existing hypertension but without CHF following first MI 3. Revascularization procedure rate (PTCA/CABG) reduced significantly with diltiazem following thrombolytic use following first MI • Cardizem CD [and its generic equivalent]are indicated for vasospastic angina, chronic stable angina, and essential hypertension. • Regular release diltiazem is indicated for vasospastic and chronic stable angina. • Dilacor XR [and its generic equivalent] and Tiazac are indicated for chronic stable angina and hypertension. • The formulations of diltiazem that is dosed BID, as well as Cardizem LA, are indicated for hypertension only. • An SNDA has been filed for the indication of angina for Cardizem LA • Cardizem LA is the only long acting diltiazem product that is labeled to be given either in the morning or evening; however the study of another chronotropic CCB (Covera HS® in the CONVINCE trial) did not shown superiority in outcomes with a chronotropic agent. • The pharmacokinetic profiles of Tiazac, Dilacor XR Cardizem CD are significantly different according to studies funded by Bioavail (Cardizem CD).

Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study.

Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlof B, Karlberg BE.

Lancet. 2000 Jul 29;356(9227):359-65.
Department of Public Health and Social Sciences, University of Uppsala, Sweden.

BACKGROUND: Calcium antagonists are a first-line treatment for hypertension. The effectiveness of diltiazem, a non-dihydropyridine calcium antagonist, in reducing cardiovascular morbidity or mortality is unclear. We compared the effects of diltiazem with that of diuretics, beta-blockers, or both on cardiovascular morbidity and mortality in hypertensive patients. METHODS: In a prospective, randomised, open, blinded endpoint study, we enrolled 10,881 patients, aged 50-74 years, at health centres in Norway and Sweden, who had diastolic blood pressure of 100 mm Hg or more. We randomly assigned patients diltiazem, or diuretics, beta-blockers, or both. The combined primary endpoint was fatal and non-fatal stroke, myocardial infarction, and other cardiovascular death. Analysis was done by intention to treat. FINDINGS: Systolic and diastolic blood pressure were lowered effectively in the diltiazem and diuretic and beta-blocker groups (reduction 20.3/18.7 vs 23.3/18.7 mm Hg; difference in systolic reduction p<0.001). A primary endpoint occurred in 403 patients in the diltiazem group and in 400 in the diuretic and beta-blocker group (16.6 vs 16.2 events per 1000 patient-years; relative risk 1.00 [95% CI 0.87-1.15], p=0.97). Fatal and non-fatal stroke occurred in 159 patients in the diltiazem group and in 196 in the diuretic and beta-blocker group (6.4 vs 7.9 events per 1000 patient-years; 0.80 [0.65-0.99], p=0.04) and fatal and non-fatal myocardial infarction in 183 and 157 patients (7.4 vs 6.3 events per 1000 patient-years; 1.16 [0.94-1.44], p=0.17). INTERPRETATION: Diltiazem was as effective as treatment based on diuretics, beta-blockers, or both in preventing the combined primary endpoint of all stroke, myocardial infarction, and other cardiovascular death.

The effect of diltiazem on mortality and reinfarction after myocardial infarction. The Multicenter Diltiazem Postinfarction Trial Research Group.

N Engl J Med. 1988 Aug 18;319(7):385-92.

[No authors listed]

We studied the effect of diltiazem on mortality and reinfarction in 2466 patients with previous infarction from 38 hospitals in the United States and Canada. The patients were randomly assigned to receive diltiazem (240 mg per day, n = 1234) or placebo (n = 1232) and followed for 12 to 52 months (mean, 25). Total mortality rates were nearly identical among the two treatment groups (167 and 166, respectively), as were cumulative mortality rates. There were 11 percent fewer first recurrent cardiac events (death from cardiac causes or nonfatal reinfarction) in the diltiazem group than in the placebo group (202 vs. 226; Cox hazard ratio, 0.90; 95 percent confidence limits, 0.74 and 1.08). A significant ($P = 0.0042$) bidirectional interaction between diltiazem and pulmonary congestion was observed on x-ray examination. In 1909 patients without pulmonary congestion, diltiazem was associated with a reduced number of cardiac events (hazard ratio, 0.77; 95 percent confidence limits, 0.61 and 0.98); in 490 patients with pulmonary congestion, diltiazem was associated with an increased number of cardiac events (hazard ratio, 1.41; 95 percent confidence limits, 1.01 and 1.96). A similar pattern was observed with respect to the ejection fraction, which was dichotomized at 0.40. Thus, diltiazem exerted no overall effect on mortality or cardiac events in this population of patients with previous infarction. This neutral effect reflected a diltiazem-related reduction in cardiac events in the majority of patients without left ventricular dysfunction and an increase in such events in the minority of patients with left ventricular dysfunction.

Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics.

Eradiri O, Midha KK.
Int J Clin Pharmacol Ther. 1997 Sep;35(9):369-73.

Research and Development Division, Biovail Corporation International, Mississauga, Ontario, Canada.

Diltiazem has proven to be an effective antihypertensive and antianginal agent, due to its potent calcium channel blocking activity. The present study was conducted to compare the bioavailability of a new extended release diltiazem HCl capsule formulation (Tiazac) with 2 other currently marketed products (Cardizem CD and Dilacor XR). Fourteen healthy male subjects participated in this randomized, 3-period, multiple daily dose (240 mg for 7 days), crossover bioavailability study. ANOVA and multiple comparison tests showed the parent drug AUC0-tau to be significantly higher after daily dosing with Tiazac than with the other 2 marketed products, but the diltiazem Cmin values were not significantly different between the 3 formulations. Between 5 and 12 hours after drug administration, mean plasma diltiazem levels for Tiazac capsules were found to be significantly higher than those of the 2 other products tested. Comparison of plasma concentrations of metabolites for the 3 capsule formulations by ANOVA and multiple comparison tests showed similar trends as in the case of parent drug concentrations. These findings may be clinically important as higher and more consistent plasma concentrations of diltiazem, and its active metabolite during daytime are needed to counteract higher blood pressures in hypertensive patients due to circadian variations. The new extended release product of diltiazem HCl was found to exhibit significantly differing pharmacokinetics of the parent compound compared to either of the other 2 products tested.

Relative bioavailability of Cardizem CD and Tiazac controlled-release diltiazem dosage forms after single and multiple dosing in healthy volunteers.

Dimmitt DC, Bhargava VO, Arumugham T, Eller M, Weir SJ.
Am J Ther. 1998 May;5(3):173-9.

North America Pharmacokinetics, Hoechst Marion Roussel, P.O. Box 9627, F4-M3112, Kansas City, MO 64134, USA.

The purpose of this study was to determine the relative bioavailability of Cardizem CD compared to Tiazac after single and multiple doses. Twenty-three healthy males were enrolled in this open-label, two-way, complete crossover investigation. During each of the two treatment periods, a single 240-mg dose of diltiazem HCl was given in the morning on study day 1, then once daily on days 3 through 9. Serial plasma samples were obtained and pharmacokinetic parameters were calculated from the single-dose and steady-state concentration-time profiles. After single doses, mean diltiazem maximum plasma concentration (Cmax) was 46% higher with the Tiazac formulation compared with Cardizem CD, and the mean area under the plasma concentration-time profile (AUC) was 19% higher with Tiazac. At steady-state, similar Cmax and AUC for the 24-hour dosing interval were found for Cardizem CD and Tiazac. However, Tiazac produced a 21% lower diltiazem minimum plasma concentration, a 28% lower trough concentration (the concentration in the plasma sample obtained just before the daily dose was given), and a 1.5-times higher fluctuation in maximum to minimum diltiazem plasma concentration compared with Cardizem CD. The pharmacokinetic profiles of the two pharmacologically active diltiazem metabolites, desacetyldiltiazem and N-desmethyldiltiazem, followed that of parent drug after single and multiple doses of Cardizem CD and Tiazac. From these results, it is concluded that the pharmacokinetic profiles of Tiazac and Cardizem CD are significantly different

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)	
Characteristic	**(Phenylalkylamine)** **Calan, Isoptin, Covera, Verelan** **(Verapamil)**
Pharmacology	Verapamil locally inhibits membrane transport of calcium in the myocardial cell membrane which results in negative inotropic effects and antiarrhythmic properties. The antiarrhythmic activity of verapamil is due to its ability to delay impulse transmission through the atrioventricular (AV) node by direct action; the drug blocks antegrade AV-nodal conduction, without a significant effect on retrograde conduction in the AV node or accessory pathways. Intracellular reductions in calcium concentration in cardiac cells and smooth muscle cells of coronary and peripheral vasculature result in dilation of coronary and peripheral arteries and arterioles, a reduced heart rate, decreased myocardial contractility, slowed AV conduction and decreases in blood pressure.
Manufacturer	**Verelan PM**: Schwarz Pharma **Covera HS:** Searle All other available generically
Date of FDA Approval	**Verelan PM**: Nov. 25, 1998 **Covera HS**: Feb. 26, 1996 All others available generically
Generic available?	Verelan PM and Covera HS: not available generically Yes for all other formulations
Dosage forms / route of admin.	Calan IR Tablets: 40, 80,120 mg Covera-HS Tablets, extended release: 180, 240 mg Calan SR Tablets, sustained release: 120, 180 mg, 240 mg Isoptin SR Tablets, sustained release: 120, 180, 240 mg Generic Capsules, extended release: 120, 180, 240 mg Verelan PM Capsules, sustained release: 100, 200, 300 mg Verelan Capsules, sustained release: 120, 180, 240, 360 mg Verapamil Injection: 2.5 mg/mL;in 2 and 4 mL vials, amps, and syringes
Dosing frequency	Immediate Release ▪ TID (Angina) ▪ TID or QID (Arrhythmias) ▪ TID (Essential hypertension) Sustained release ▪ QD (Essential hypertension)

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)	
Characteristic	**(Phenylalkylamine)** **Calan, Isoptin, Covera, Verelan** **(Verapamil)**
General Dosing Guidelines	Immediate Release: Individualize. Max 480mg/day. (Adults) Angina: 80 to 120mg three times daily. Digitalized patients with chronic AF: 240 to 320mg/day in 3 or 4 divided doses. Prophylaxis of PSVT: 240 to 480mg/day in 3 or 4 divided doses. Hypertension: Start at 80mg 3 times daily; titrate as necessary. Covera HS: Start at 180mg once daily at bedtime; increase as necessary to max 480mg once daily at bedtime. Calan SR and Isoptin SR: Individualize. (Adults) Start at 180mg in morning; titrate as necessary. (Elderly) Start at 120mg in morning. Max 480mg/day. Verelan PM: 200mg once daily at bedtime. Increase to 300mg, then 400mg once daily as needed and tolerated. Some patients respond to 100mg once daily. Verelan: (Adults) Individualize by titration. Usually 240mg/day in morning. 120mg/day may suffice with increased response. Max 480mg/day.
Pediatric Labeling	None
Indications	▪ Angina: Treatment of vasospastic (Prinzmetal's variant), chronic stable (classic effort-associated) and unstable (crescendo, preinfarction) angina. ▪ Arrhythmias: With digitalis to control ventricular rate at rest and during stress in chronic atrial flutter or fibrillation. May use for prophylaxis of repetitive paroxysmal supraventricular tachycardia (PSVT). ▪ Essential hypertension. Sustained release: Only for management of essential hypertension.
Other studied uses	▪ Migraine propylaxis ▪ Panic attacks ▪ Pulmonary hypertension ▪ Esophageal spasma ▪ Nephropathy

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)	
Characteristic	**(Phenylalkylamine) Calan, Isoptin, Covera, Verelan (Verapamil)**
Contraindications	▪ Hypersensitivity to the drug in question ▪ Sick sinus syndrome (bepridil, diltiazem, verapamil) ▪ 2nd or 3rd degree heart block – except with functioning pacemaker (bepridil, diltiazem, verapamil) ▪ Hypotension < 90 mm Hg systolic (bepridil, diltiazem, verapamil) ▪ Acute MI and pulmonary congestion (diltiazem) ▪ Severe left ventricular dysfunction, cardiogenic shock, severe CHF unless related to SVT treatable with verapamil, and in patients with atrial flutter or atrial fibrillation and an accessory bypass tract. ▪ History of serious ventricular dysrhythmias, uncompensated cardiac insufficiency, congenital QT interval prolongation, combination with other drugs that increase QT interval (bepridil)
Drug interactions	Barbiturates, Calcium salts, Dantrolene, Erythromycin, Hydantoins, Quinidine, Rifampin, Sulfinpyrazone, Vitamin D, Anticoagulants, Beta blockers, Carbamazepine, Digitalis glycosides, Etomidate, Fentanyl, Lithium, Magnesium sulfate, parenteral, Nondepolarizing muscle relaxants, Prazosin, Theophyllines
Major AEs / Warnings	Major AEs : Constipation, nausea, dizziness, hypotension, headache, edema, CHF/pulmonary edema, fatigue, dyspnea, bradycardia, AV block, rash, flushing. Warnings: ▪ Pregnancy: Category C, Induction of new serious arrhythmias (bepridil), Hypotension, Congestive heart failure, Cardiac conduction, Premature ventricular contractions (PVCs), Antiplatelet effects, Withdrawal syndrome, Agranulocytosis, Hepatic/ Renal function impairment, Increased angina, Increased intracranial pressure, Acute hepatic injury, Edema
Dosage adjustment in key populations	▪ Hepatic function impairment: The pharmacokinetics, bioavailability and patient response to verapamil and nifedipine may be significantly affected by hepatic cirrhosis. Since amlodipine, diltiazem, nicardipine, bepridil, felodipine and nimodipine are extensively metabolized by liver, use with caution in impaired hepatic function or reduced hepatic blood flow. ▪ Renal function impairment: Administer verapamil cautiously to patients with impaired renal function. Nifedipine - Plasma concentration is slightly increased in patients with renal impairment. Nicardipine - Mean plasma concentrations, AUC and maximum concentration were approximately twofold higher in patients with mild renal impairment. Doses must be adjusted. Use bepridil with caution in patients with serious renal disorders since the metabolites of bepridil are excreted primarily in the urine.

Non-Dihydropyridine Calcium Channel Antagonists/Blockers (NDHP-CCB)	
Characteristic	**(Phenylalkylamine) Calan, Isoptin, Covera, Verelan (Verapamil)**
Pipeline Agents	▪ T-channel blockers: The plasma membrane calcium channels, which include the L- and T-type channels, are of clinical interest for pharmacologic therapy. T-type calcium channels, which activate contraction in vascular smooth muscle but have little or no role in cardiac excitation-contraction coupling, appear to be involved in signal transduction pathways that promote cell growth and proliferation. Calcium channel blockers that selectively block T-type calcium channels, therefore, offer a novel approach to cardiovascular drug therapy. 1. DP-3005 made by Diakron is the pro-type T-channel blocker in development. Note: Posicor® (mibefradil) was a combined L and T- channel blocker that was withdrawn from the market in June of 1998.
Unique Features/ Advantages /Summary/Efficacy	• Verelan PM (verapamil HCl) and Covera HS (verapamil HCl) provide chronotherapy for hypertension. A major objective of chronotherapy for hypertension is to deliver the drug in higher concentrations during the early-morning post-awakening period, when BP is highest, and in lesser concentrations during the middle of a sleep cycle, when BP is low. Traditional sustained-release pharmacologic agents, which deliver a near-constant drug concentration, were not designed to complement the circadian pattern. However, this novel delivery system with its emphasis on chronotherapy has not proven to be superior to other agents in clinical trials (ie CONVINCE trial). • Regular release verapamil is indicated for vasospastic angina, chronic stable angina, unstable angina, hypertension, and prophylaxis of paroxysmal supraventricular tachycardia/rate control of atrial fibrillation and flutter in association with digitalis. • Each of the sustained release formulations (including Verelan PM) is indicated for hypertension. • Covera-HS is indicated for chronic stable angina and unstable angina at rest in addition to hypertension.

Treatment with verapamil during and after an acute myocardial infarction: a review based on the Danish Verapamil Infarction Trials I and II. The Danish Study Group on Verapamil in Myocardial Infarction.

Hansen JF.

J Cardiovasc Pharmacol. 1991;18 Suppl 6:S20-5.

Department of Cardiology, Hvidovre Hospital, Denmark.

The effect of verapamil on death and reinfarction after an acute myocardial infarction was studied in two double-blind, randomized, placebo-controlled multicenter trials, the Danish Verapamil Infarction Trials I and II (DAVIT I and II). The studies demonstrated that verapamil 360 mg/day from the 2nd week after an acute myocardial infarction, prevented death and reinfarction. Meta-analyses of the results of DAVITs I and II resulted in a reduction of pooled ratios of 22% (95% confidence limits 1-37, p = 0.04) for death, 21% (5-35, p = 0.02) for first major events (first reinfarction or death), and 27% (6-43, p = 0.02) for first reinfarctions. The effect of verapamil was to prevent myocardial ischemia and reduce sudden death and reinfarction. It is concluded that long-term treatment with verapamil after an acute myocardial infarction may be recommended with the object of reducing overall mortality, major events and reinfarction

Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial.

Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH Jr, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ; CONVINCE Research Group.

JAMA. 2003 Apr 23-30;289(16):2073-82.

CONTEXT: Hypertensive patients are often given a calcium antagonist to reduce cardiovascular disease risk, but the benefit compared with other drug classes is controversial. OBJECTIVE: To determine whether initial therapy with controlled-onset extended-release (COER) verapamil is equivalent to a physician's choice of atenolol or hydrochlorothiazide in preventing cardiovascular disease. DESIGN, SETTING, AND PARTICIPANTS: Double-blind, randomized clinical trial conducted at 661 centers in 15 countries. A total of 16 602 participants diagnosed as having hypertension and who had 1 or more additional risk factors for cardiovascular disease were enrolled between September 1996 and December 1998 and followed up until December 31, 2000. After a mean of 3 years of follow-up, the sponsor closed the study before unblinding the results. INTERVENTION: Initially, 8241 participants received 180 mg of COER verapamil and 8361 received either 50 mg of atenolol or 12.5 mg of hydrochlorothiazide. Other drugs (eg, diuretic, beta-blocker, or an angiotensin-converting enzyme inhibitor) could be added in specified sequence if needed. MAIN OUTCOME MEASURES: First occurrence of stroke, myocardial infarction, or cardiovascular disease-related death. RESULTS: Systolic and diastolic blood pressure were reduced by 13.6 mm Hg and 7.8 mm Hg for participants assigned to the COER verapamil group and by 13.5 and 7.1 mm Hg for partcipants assigned to the atenolol or hydrochlorothiazide group. There were 364 primary cardiovascular disease-related events that occurred in the COER verapamil group vs 365 in atenolol or hydrochlorothiazide group (hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.88-1.18; P =.77). For fatal or nonfatal stroke, the HR was 1.15 (95% CI, 0.90-1.48); for fatal or nonfatal myocardial infarction, 0.82 (95% CI, 0.65-1.03); and for cardiovascular disease-related death, 1.09 (95% CI, 0.87-1.37). The HR was 1.05 (95% CI, 0.95-1.16) for any prespecified cardiovascular disease-related event and 1.08 (95% CI, 0.93-1.26) for all-cause mortality. Nonstroke hemorrhage was more common with participants in the COER-verapamil group (n = 118) compared with the atenolol or hydrochlorothiazide group (n = 79) (HR, 1.54 [95% CI, 1.16-2.04]; P =.003). More cardiovascular disease-related events occurred between 6 AM and noon in both the COER verapamil (99/277) and atenolol or hydrochlorothiazide (88/274) groups; HR, 1.15 (95% CI, 0.86-1.53). CONCLUSIONS: The CONVINCE trial did not demonstrate equivalence of a COER verapamil-based antihypertensive regimen compared with a regimen beginning with a diuretic or beta-blocker. When considered in the context of other trials of calcium antagonists, these data indicate that the effectiveness of calcium-channel therapy in reducing cardiovascular disease is similar but not better than diuretic or beta-blocker treatment.

Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. VHAS Investigators.

Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A, Zanchetti A.

J Hypertens. 1997 Nov;15(11):1337-44.

Cattedra di Semeiotica e Metodologia Medica, University of Brescia, Italy.

OBJECTIVE: The Verapamil in Hypertension and Atherosclerosis Study (VHAS) is a prospective randomized study the objective of which was to compare the long-term effects of verapamil and chlorthalidone on the blood pressure, clinical safety, and the progression/regression of carotid wall lesions in members of a large population of hypertensive patients. DESIGN: After a 3-week placebo run-in period, 1414 hypertensive patients [692 men and 722 women, aged 53.2 +/- 7 years, blood pressure 168.9 +/- 10.5/ 102.2 +/- 5.0 mmHg (means +/- SD)] were assigned randomly to be administered either 240 mg sustained-release verapamil (n = 707) or 25 mg chlorthalidone (n = 707) once a day for 2 years. The study design was double blind for the first 6 months and open thereafter. 25-50 mg/day captopril were added to the treatment of non-responding patients; subsequently, patients not responding to combined therapy were switched to any therapy chosen by the treating doctors (free therapy). The blood pressure of the sitting subject, heart rate, and a standard clinical safety profile (electrocardiogram, laboratory tests, adverse events, cardiovascular events, and deaths) were assessed regularly throughout the study. RESULTS: After 2 years the systolic and diastolic blood pressures were reduced significantly in members of both treatment groups (by 16.3/16.6% with verapamil and by 16.9/16.2% with chlorthalidone, both by analysis of variance, P < 0.0001). The patients for whom we added captopril treatment constituted 22.6% of the verapamil and 26.2% of the chlorthalidone group; while 11.6 and 12.2% of patients in these groups, respectively, were administered free therapy. Normalization of the diastolic blood pressure (to < or = 90 mmHg or to < or = 95 mmHg with a > or = 10% decrease) was achieved for 69.3% of the verapamil and 66.9% of the chlorthalidone group. A decrease in heart rate (by 5.8%) occurred in members of the verapamil group only. A decrease in total serum cholesterol (from 223.6 to 216.9 mg/dl, P < 0.01) and in the total cholesterol: high-density lipoprotein cholesterol ratio (from 4.9 to 4.5, P < 0.01) was noted for the verapamil group only, whereas significantly greater rates of hyperuricemia (plasma urate > 7.0 mg/dl; 10.8 versus 3.9%) and hypokalemia (serum K < 3.5 mmol/l; 24.6 versus 4.4%) were observed for the chlorthalidone group (P < 0.01, versus verapamil for both). Adverse events were reported by 32.5% of patients treated with verapamil and by 33.4% of those treated with chlorthalidone. The most frequent adverse events were constipation in members of the verapamil group (13.7%) and asthenia in members of the chlorthalidone group (8.5%). In total 315 dropped out (153 from the verapamil and 162 from the chlorthalidone group). The occurrence of cardiovascular events was similar for both treatments (42 events for verapamil and 43 for chlorthalidone, NS). CONCLUSION: Similar antihypertensive efficacies, tolerabilities and cardiovascular event rates were observed with verapamil and with chlorthalidone. However, treatment with chlorthalidone was associated with significantly higher incidences of hyperuricemia and hypokalemia than was treatment with verapamil.

Alpha/ Beta-Blockers (a_1, $ß_1$, $ß_2$ blockers)		
Characteristic	**Coreg (Carvedilol)**	**Trandate, Normodyne (Labetalol)**
Pharmacology	Carvedilol is a racemic mixture with non-selective ß-adrenergic receptor blocking activity and a-adrenergic receptor blocking activity with no intrinsic sympathomimetic activity. Carvedilol reduces cardiac output, reduces exercise or ß-adrenergic agonist induced tachycardia, and reduces reflex orthostatic tachycardia. Significant ß-blocking effect is usually seen within 1 hour of administration. Carvedilol also attenuates the pressor effects of phenylephrine, causes vasodilation, and reduces peripheral vascular resistance. These effects are usually seen within 30 minutes of administration. Because of the a-blocking activity, blood pressure is lowered more in standing than in supine position, and symptoms of postural hypotension can occur (with rare occasions of syncope).	Labetalol combines both selective, competitive post-synaptic a_1-adrenergic blocking and nonselective, competitive ß-adrenergic blocking activity. Because of the a-blocking activity, blood pressure is lowered more in standing than in supine position, and symptoms of postural hypotension can occur (with rare occasions of syncope). Labetalol blunts exercise-induced increases in blood pressure and heart rate with dose-related response. Labetolol produces dose-related falls in BP without reflex tachycardia or significant reduction in heart rate. Although ß-blockade is beneficial in treating angina and hypertension, patients with severely damaged hearts may depend on sympathetic drive for adequate ventricular function. ß-blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction.
Manufacturer	Glaxo Smith Kline	Multiple generic manufacturers
Date of FDA Approval	9/14/95	Available generically
Generic available?	No	Yes
Dosage forms / route of admin.	Tablets: 3.125 mg, 6.25 mg, 12.5 mg, 25 mg	Generic Tablets: 100 mg, 200 mg, 300mg Trandate, And Normodyne: 100 mg, 200 mg, 300mg Tablets, Trandate, Normodyne and Generic Injection: 5 mg/ml

Alpha/ Beta-Blockers (a$_1$, ß$_1$, ß$_2$ blockers)		
Characteristic	**Coreg (Carvedilol)**	**Trandate, Normodyne (Labetalol)**
Dosing frequency	BID	BID
Generalized Dosing Guidelines	**Hypertension** ▪ Initial: 6.25 mg BID, may increase to 12.5 mg BID, if needed. May be adjusted upward to 25 mg BID if tolerated and needed. The full antihypertensive effect of carvedilol is seen within 7 to 14 days. Total daily dose should not exceed 50 mg. ▪ Addition of a diuretic to carvedilol or carvedilol to a diuretic can be expected to produce additive effects. **Congestive Heart Failure** ▪ Starting dose of carvedilol is 3.125 mg BID for 2 weeks. If tolerated, it may be increased to 6.25 mg BID. Dosing should be doubled every 2 weeks to the highest level tolerated. Maximum is 25 mg BID in patients < 85 kg and 50 mg BID in patients > 85 kg. **Left Ventricular Dysfunction following Myocardial Infarction** ▪ Initial: 6.25mg BID, may increase after 3-10 days to 12.5mg BID to target dose. Maximum recommended dose 25mg BID.	**Hypertension** ▪ Initial: 100 mg BID, alone or added to a diuretic. After 2 or 3 days, titrate dosage in increments of 100 mg BID, every 2-3 days. Full antihypertensive effect is usually seen within the first 1-3 hours of initial dose or dose increment. ▪ Maintenance: 200-400 mg BID. Patients with severe hypertension may require 1.2-2.4 g/day. Should side effects (principally nausea or dizziness) occur with twice-daily dosing, the same total daily dose given 3 times/day may improve tolerability. Titration increments should not exceed 200-mg BID. ▪ Elderly: Elderly patients will generally require lower maintenance dosages.

Alpha/ Beta-Blockers (a1, ß1, ß2 blockers)		
Characteristic	**Coreg (Carvedilol)**	**Trandate, Normodyne (Labetalol)**
FDA labeled Indications	▪ Hypertension ▪ Congestive heart failure (mild to severe) ▪ Left ventricular dysfunction following myocardial infarction	▪ Hypertension
Pediatric Labeling	Not FDA approved – CHF: 0.09mg/kg BID increase at 2 week intervals. Maximum recommended dose 50mg/day	Not FDA approved – Hypertension: 3-15 years of age; IV - Bolus 0.22-1mg/kg; continuous infusion – 0.25-1.5mg/kg/hr
Other studied uses	▪ Appears to be beneficial in the treatment of angina pectoris (25-50 mg BID) ▪ Anxiety disorders	▪ Has effectively lowered BP and relieved symptoms in patients with pheochromocytoma; higher IV doses may be required. However, paradoxical hypertensive responses have occurred; therefore, use caution when administering labetalol. ▪ Labetalol has been used in clonidine withdrawal hypertension. ▪ Has been used in angina (initial dose 100-200mg BID titrated to maximum of 1200mg daily in 2 divided doses); Angina with mild to moderate heart failure initiate at 50mg BID and titrate as needed. Not recommended in angina with severe heart failure
Contraindications	Bronchial asthma or related bronchospastic conditions; second- or third-degree AV block; sick sinus syndrome (unless a permanent pacemaker is in place); cardiogenic shock; severe bradycardia; severe hepatic impairment; hypersensitivity to the drug.	Bronchial asthma; overt cardiac failure; greater than first-degree heart block; cardiogenic shock; severe bradycardia.
Drug interactions	Antidiabetic agents, Calcium channel blockers, Catecholamine- depleting agents (e.g., reserpine), Clonidine, Digoxin, Cimetidine, Rifampin, cyclosporine	Beta-adrenergic agonist, Calcium channel blockers (diphenylalkylamines), Nitroglycerin, Tricyclic antidepressants, Cimetidine, Glutethimide, Halothane

Alpha/ Beta-Blockers (a_1, $ß_1$, $ß_2$ blockers)		
Characteristic	**Coreg (Carvedilol)**	**Trandate, Normodyne (Labetalol)**
Major AEs / Warnings	Major AEs (not all inclusive) ▪ Carvedilol is well tolerated at doses up to 50 mg daily. Most adverse events reported were of mild-moderate severity. Trials comparing carvedilol (≤ 50 mg) to placebo, 4.9% of carvedilol patients discontinued for adverse events vs 5.2% of placebo patients. ▪ Hematologic – Thrombocytopenia (1-2% of patients) ▪ Postural hypotension ▪ Cardiovascular – Bradycardia, palpitations, syncope, edema, angina, atrioventricular block, hypertension, hypotension, intermittent claudication, and shock ▪ CNS – Fatigue, headache, insomnia, somnolence, lightheadedness, dizziness, and myoclonus ▪ Endocrine/Metabolic – Hyperglycemia has been reported with carvedilol use in patients being treated for CHF. Blood glucose levels seem to be unaffected in type II diabetes patients. Type II diabetes has developed in hypertensive patients being treated with carvedilol. Hypertriglyceride and weight gain have occurred with carvedilol use. ▪ Gastrointestinal – Nausea, diarrhea, abdominal pain and vomiting ▪ Kidney/Genitourinary – Erectile dysfunction ▪ Hepatic – Hepatotoxicity, apparently reversible and rare, has occurred during treatment with carvedilol. ▪ Ocular – Non-specific visual changes ▪ Respiratory – Bronchospasm, rhinitis, pharyngitis and dyspnea ▪ Dermatological – Rash and pruritus along with associated effects of Stevens-Johnson syndrome have been associated with carvedilol therapy ▪ Musculoskeletal – Myalgia, joint and back pain Warnings (not all inclusive) ▪ Pregnancy: Category C; Bronchial asthma; hepatotoxicity; Hypotension and postural hypotension; Diabetes and hypoglycemia; Hepatic function impairment; hypersensitivity	Major AEs (not all inclusive) ▪ Labetalol is usually well tolerated. Most adverse effects have been mild and transient. With oral labetalol, most occur early in the course of treatment. Discontinuation was required in 7% of all patients in controlled clinical trials. ▪ CNS - Fatigue; headache; drowsiness; paresthesias; rare instances of syncope. ▪ Dermatologic - Rashes such as generalized maculopapular, lichenoid, urticarial; bullous lichen planus; psoriasiform; facial erythema; reversible alopecia. ▪ GI - Diarrhea; cholestasis with or without jaundice; reversible increases in serum transaminases. ▪ GU - Ejaculation failure; impotence; priapism; difficulty in micturition; acute urinary bladder retention; Peyronie's disease. ▪ Musculoskeletal - Asthenia; muscle cramps; toxic myopathy. ▪ Respiratory - Dyspnea; bronchospasm. ▪ Miscellaneous - Systemic lupus erythematosus; positive antinuclear factor (ANF); antimitochondrial antibodies; edema; nasal stuffiness; fever; vision abnormality; dry eyes. Warnings (not all inclusive) ▪ Pregnancy: Category C; Cardiac failure; Withdrawal; Nonallergic bronchospasm; diabetes and hypoglycemia; Hepatic toxicity; hepatic function impairment.

Alpha/ Beta-Blockers (a_1, ß$_1$, ß$_2$ blockers)

Characteristic	**Coreg** **(Carvedilol)**	**Trandate, Normodyne** **(Labetalol)**
Pharmacokinetic issues	Carvedilol is rapidly and extensively absorbed following oral administration. Bioavailability is limited to 25%-35% due to significant amount of first-pass metabolism. Plasma concentrations are proportional to the dose administered. When administered with food, absorption rate is slowed with no significant decrease in extent of bioavailability. Often carvedilol is given with food to decrease the incidence of orthostatic hypotension. Carvedilol is more than 98% bound to plasma protein (primarily albumin).	Oral labetalol is completely absorbed with peak plasma levels occurring in 1-2 hours. The peak affects of a single oral dose occur within 2-4 hours. The maximum, steady-state BP response with oral, BID dosing occurs within 24 to 72 hours. Due to extensive first-pass metabolism, absolute bioavailability is 25%; this is increased by food and in the elderly.
Dosage adjustment in key populations	▪ Hepatic function impairment: Use of carvedilol in patients with clinically manifest hepatic impairment is not recommended. If used in patients with liver disease, dose should be 20% of normal recommended dose. ▪ Although carvedilol is metabolized primarily by the liver, plasma concentrations have been reported to be increased in patients with renal impairment. ▪ Elderly: Plasma levels of carvedilol average approximately 50% higher in the elderly compared with younger subjects.	▪ Hepatic function impairment: Use with caution; drug metabolism may be diminished. The relative bioavailability in hepatically impaired patients is increased because of decreased "first-pass" metabolism. ▪ Elderly: Elderly patients will generally require lower maintenance dosages
Pipeline Agents	▪ Nebivolol (no brand name, Bertek): Unlike other currently marketed beta blockers, nebivolol combines a high degree of beta$_1$ selectivity with nitric oxide – dependent vasodilation. This dual mechanism of action is considered unique to the compound. Nebivolol is currently marketed in 30 countries throughout Europe and Central America ▪ Celiprolol (no brand name): is a cardioselective beta-adrenergic blocking agent with alpha-2 receptor blocking activity and partial beta- 2 agonist vasodilatory properties. Celiprolol has been studied in heart failure and hypertension.	
Advantages/Unique Features	▪ Carvedilol has shown to reduce mortality in patients with mild to severe heart failure, post-myocardial infarction with EF< 40% if administered within 21 days following an MI. It is effective in lowering blood pressure in hypertensive patients. Adverse effects are similar to other ß-blockers. Head-to-head studies have been performed with metoprolol.	▪ Labetalol has been shown to be effective as an antihypertensive agent. Adverse effect profile is similar to other ß-blockers.

Alpha/ Beta-Blockers (a_1, $ß_1$, $ß_2$ blockers)		
Characteristic	**Coreg (Carvedilol)**	**Trandate, Normodyne (Labetalol)**
Advantages/Unique Features	▪ It is worthy to note that both agents have an $alpha_1$ adrenergic blocking component combined with their non-selective beta blockade. In March 2002, the fourth arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) sponsored by the NHLBI halted the arm containing the $alpha_1$ adrenergic blocker, Cardura ® (doxazosin). Data revealed that Cardura® was less effective than the more traditional diuretic in reducing some forms of cardiovascular disease, such as congestive heart failure and that users of the drug had a 25% more cardiovascular events and were twice as likely to be hospitalized for heart failure than users of the diuretic chlorthalidone.	
Summary/Efficacy	▪ *See last page*	

Beta Blockers ($ß_1$ selective)			
Characteristic	**Sectral (acebutolol)**	**Tenormin, Tenoretic (atenolol)**	**Kerlone (betaxolol)**
Pharmacology	Acebutolol is a cardioselective ß-adrenergic receptor blocker with weak intrinsic sympathomimetic properties (ISA) and low membrane stabilizing effects (MSA). $ß_1$ selectivity diminishes as the dose increases.	Atenolol is a long-acting cardioselective ß-adrenergic receptor blocker with no intrinsic sympathomimetic activity (ISA) or membrane stabilizing properties (MSA). Selectivity diminishes as dose increases. Patients with obstructive airway disease may be given atenolol in small doses, but if atenolol is given in full doses ß-adrenergic agonists should also be given.	Betaxolol is a cardioselective ß-adrenergic receptor blocker with no ISA and weak MSA. One report has indicated that routinely used doses of betaxolol were associated with a partial loss of $ß_1$ selectivity, although $ß_2$ blockade was significantly less than that of propranolol.
	Beta-blockers are effective in the treatment of angina because they decrease heart rate, blood pressure, contractile force, and cardiac work load which reduces myocardial oxygen consumption, enhances coronary artery blood flow and improves myocardial perfusion. The antihypertensive mechanism of beta-blockers may be related to decreased cardiac output, reduced adrenergic energy, and inhibition of renin release. Beta-blockers exert an antiarrhythmic effect through inhibition of adrenergic stimulation of cardiac pacemaker potentials and slowing conduction through the atrioventricular node. Some supraventricular arrhythmias respond well to beta-blockers because they depress sinus node automaticity and suppress atrioventricular nodal conduction. The MSA (membrane stabilizing activity) may account for the antiarrhythmic activity by depressing excitability, prolonging refractory period and delaying conduction. Beta-blockers with intrinsic ISA offer advantage over other agents by reducing systemic blood pressure and total peripheral resistance without inducing important changes in heart rate, cardiac output, and renal blood flow.		
Manufacturer	Multiple generic manufacturers	Multiple generic manufacturers	Searle
FDA Approval Date	Off patent	Off patent	10/27/89
Generic available?	Yes	Yes-Tenormin, Tenoretic	No
Dosage forms / route of admin.	Capsules 200, 400 mg	Atenolol Tablets 25, 50, 100 mg Atenolol/chlorthalidone: 50/25, 100/25	Tablets 10, 20 mg
Dosing frequency	QD, BID,	QD, BID	QD
Pediatric Labeling	▪ Not FDA approved	▪ Not FDA approved – Pediatric Arrhythmias: 0.3-1.4mg/kg/day as a single daily dose, increase by 0.5mg/kg/day q3-4 days to maximum 2mg/kg/day	▪ Not FDA approved

Beta Blockers (ß$_1$ selective)			
Characteristic	**Sectral (acebutolol)**	**Tenormin, Tenoretic (atenolol)**	**Kerlone (betaxolol)**
Generalized Dosing Guidelines	▪ Ventricular Arrhythmias: initiate with 400mg daily (2 divided doses) individualize dose with gradual increase. Maintenance 600-1200 mg daily (2-3 divided doses) ▪ Hypertension: initiate with 400mg daily individualize with gradual increase. Maintenance 400-800mg daily. Some patients have achieved control with 200mg daily. Maximum recommended dose 1200mg (2 divided doses) ▪ Beta-1 selectivity decreases w/higher doses	▪ Angina: initiate with 50mg daily, titrate by 50mg at weekly intervals to clinical effect. Maximum daily dose 200mg ▪ Hypertension: 50-100mg daily ▪ Acute MI: within 12 hours, 5mg IV over 5 minutes, 2nd 5mg dose 10 minutes later, then initiate oral with 50mg, additional 50mg 12 hours later and maintain at 100mg QD x 10 days	▪ Hypertension: initiate with 10mg daily, may increase to 20mg after 7-14 days if needed for clinical response. Maintain at 10-40mg daily. Doses up to 40mg have been well tolerated, but generally no more effective than 20mg. Most patients receive control at 20mg daily.
FDA labeled Indications	▪ Hypertension ▪ Ventricular Arrhythmias	▪ Angina Pectoris ▪ Hypertension ▪ Myocardial Infarction	▪ Hypertension
Other studied uses	▪ Angina: doses of 600-1600mg daily in 2-3 divided doses have been effective in reducing the symptoms of angina in patients with coronary heart disease. ▪ Anxiety, hypertrophic cardiomegaly, mitral valve prolapse, myocardial reinfarction prevention, thyrotoxicosis, tremors	▪ Cardiac Arrhythmias (50-100mg daily), alcohol withdrawal, anxiety, esophageal varices rebleeding, migraine prophylaxis (50-100mg daily), hypertrophic cardiomyopathy, mitral valve prolapse, Adjunct therapy in pheochromocytoma, thyrotoxicosis, tremors	▪ Angina: 5-80mg daily in 2 small studies shown to prevent ischemic attacks and increase exercise capacity ▪ Neuroleptic induced akathisia – betazolol 5-20mg daily has been beneficial in the treatment of neuroleptic induced akathisia in 2 small trials
Contraindications	Sinus bradycardia; greater than first-degree heart block; cardiogenic shock; CHF unless secondary to a tachyarrhythmia treatable with beta-blockers; overt cardiac failure; hypersensitivity to b-blocking agents. ▪ Acebutolol, carteolol: Persistently severe bradycardia. ▪ Propranolol, nadolol, timolol, penbutolol, carteolol, sotalol, and pindolol: Bronchial asthma, including severe chronic obstructive pulmonary disease. ▪ Metoprolol: Treatment of MI in patients with a heart rate < 45 BPM; significant heart block greater than first-degree (PR interval = 0.24 sec); systolic blood pressure < 100 mmHg; moderate to severe cardiac failure. ▪ Sotalol: Congenital or acquired long QT syndromes.		

Beta Blockers (β_1 selective)			
Characteristic	**Sectral (acebutolol)**	**Tenormin, Tenoretic (atenolol)**	**Kerlone (betaxolol)**
Drug interactions	Beta Blocker Class – Aluminum salts, Barbiturates, Calcium salts, Cholestyramine, Colestipol, penicillins, Rifampin, Calcium Channel Blockers, oral contraceptives, flecainide, diphenhydramine, hydroxychloroquine, NSAID's, quinidine, ciprofloxacin, clinidine, disopyramide, epinephrine, ergot alkaloids, lidocaine, nondepolarizindg muscle relaxants, prazosin, sulfonylureas Non-Selective Beta Blockers – theophylline Metoprolol, Propranolol – cimetidine, hydralazine, propafenone, SSRI's, thioamines, Thyroid hormones, benzodiazepines Propranolol – haloperidol, loop diuretics, phenothiazines, anticoagulants, gabapentin Metoprolol, Nadolol – MAO inhibitors		
Major AEs / Warnings	Adverse effects are typically physiologic consequences of antagonized beta receptors in various tissues. Most adverse effects are mild and transient and rarely require withdrawal of therapy. ▪ Bradycardia, slowed A-V conduction, exacerbation bronchospasm in asthma or COPD, Raynaud's phenomenon, intermittent claudication, sexual dysfunction ▪ All ß-blockers have the potential to mask some of the manifestations of hypoglycemia, particularly tachycardia ▪ All ß-blockers should not be discontinued abruptly so as to avoid rebound hypertension; but, should be gradually tapered if drug is not required		
Dosage adjustment in key populations	Avoid doses higher than 800mg in geriatric patients Use with caution in hepatic impairment Renal impairment; CrCl < 50ml/min – decrease dose by 50% CrCl < 25ml/min – decrease dose by 75%	Renal impairment – titrate slowly, may also increase dosing interval CrCL 15-35ml/min – maximum dose 50mg daily CrCL < 15ml/min – maximum dose 25mg daily	Reduce starting dose (5mg) in elderly. Renal impairment – initiate with 5mg and titrate to maximum of 20mg daily. CrCl < 10ml/min reduce dose by 50%
Pipeline Agents	▪ Nebivolol (no brand name, Bertek): Unlike other currently marketed beta blockers, nebivolol combines a high degree of $beta_1$ selectivity with nitric oxide – dependent vasodilation. This dual mechanism of action is considered unique to the compound. Nebivolol is currently marketed in 30 countries throughout Europe and Central America ▪ Celiprolol (no brand name): is a cardioselective beta-adrenergic blocking agent with alpha-2 receptor blocking activity and partial beta- 2 agonist vasodilatory properties. Celiprolol has been studied in heart failure and hypertension.		
Advantages/Unique Features	Beta-blockers with intrinsic sympathomimetic activity may provide a diminished antihypertensive response due to a less pronounced decrease in cardiac output and do NOT impart benefit in migraine prophylaxis or post-MI.	Atenolol has shown improved post-infarction survival – decreasing the incidence of nonfatal cardiac arrest and cardiac death as well as reducing all-cause mortality.	
Summary/Efficacy	*See last page*		

Beta Blockers (β_1 selective)		
Characteristic	**Zebeta (bisoprolol)** **Ziac (Bisoprolol plus HCTZ)**	**Lopressor, Toprol XL (metoprolol)** **Lopressor HCT (metoprolol plus HCTZ)**
Pharmacology	Bisoprolol is a cardioselective ß-adrenergic receptor blocker with no intrinsic sympathomimetic or membrane-stabilizing activity. In a comparative trial with several other beta-blocker agents, bisoprolol was found to be slightly more cardioselective than metoprolol and acebutolol.	Metoprolol is a cardioselective ß-adrenergic receptor blocker with weak membrane stabilizing activity and no intrinsic sympathomimetic activity. Metoprolol has been shown to provide beneficial effects in patients with heart failure, although the exact mechanism has not been clearly established. Metoprolol has been shown to reduce activation of the renin-angiotensin system and heart rate in patients with heart failure. Metolprolol also has antiremodeling effects on left ventricular dimensions and function. All of these effects combined may contribute to the reduction in mortality reported in patients with chronic heart failure who receive metoprolol.
	Beta-blockers are effective in the treatment of angina because they decrease heart rate, blood pressure, contractile force, and cardiac work load which reduces myocardial oxygen consumption, enhances coronary artery blood flow and improves myocardial perfusion. The antihypertensive mechanism of beta-blockers may be related to decreased cardiac output, reduced adrenergic energy, and inhibition of renin release. Beta-blockers exert an antiarrhythmic effect through inhibition of adrenergic stimulation of cardiac pacemaker potentials and slowing conduction through the atrioventricular node. Some supraventricular arrhythmias respond well to beta-blockers because they depress sinus node automaticity and suppress atrioventricular nodal conduction. The MSA (membrane stabilizing activity) may account for the antiarrhythmic activity by depressing excitability, prolonging refractory period and delaying conduction. Beta-blockers with intrinsic ISA offer advantage over other agents by reducing systemic blood pressure and total peripheral resistance without inducing important changes in heart rate, cardiac output, and renal blood flow.	
Manufacturer	Lederle – Zebeta	Toprol XL – Astra Zeneca Lopressor HCT – Geigy
FDA Approval Date	Bisoprolol – 7/31/92	Toprol XL: JAN 10, 1992 * * KV Pharmaceuticals filed an abbreviated new drug application (ANDA) to market a generic version of AstraZeneca's top-selling heart drug Toprol XL (metoprolol succinate) on 4/9/03; however litigation will most likely ensue.
Generic available?	Ziac – Yes Zebeta – No	Lopressor - Yes Toprol XL, Lopressor HCT – No
Dosage forms / route of admin.	Bisoprolol Tabs 5,10 mg Bisoprolol/HCTZ Tabs: 2.5/6.25, 5/6.25, 10/6.25	Tablets: 50, 100 mg HCT: 25/50, 50/25, 100/25, 100/50 XL: 25, 50, 100, 200 mg
Dosing frequency	QD	BID (immediate release) QD (XL)
Pediatric Labeling	▪ Not FDA approved	▪ Safety and efficacy not established in children

Beta Blockers (β_1 selective)		
Characteristic	**Zebeta, Ziac (bisoprolol)**	**Lopressor, Toprol XL, Lopressor HCT (metoprolol)**
Generalized Dosing Guidelines	▪ Hypertension: initiate with 2.5-5mg daily, titrate to maintenance dose of 2.5-20mg daily. Maximum recommended dose 40mg	**Toprol XL** **Hypertension** – initiate with 50-100mg daily increase at 1-2 week intervals to 100-400mg daily. **Angina** – initiate with 100mg daily titrate at 1 week intervals to 100-400mg daily. **CHF** – NYHA Class II initiate with 25mg daily; NYHA Class III or IV initiate with 12.5mg daily – double dose every 2 weeks to highest tolerated dose – not to exceed 400mg daily **Immediate release** **Hypertension** – initiate with 50-100mg daily (in 2 divided doses) allow 1-2 weeks for optimal hypertensive effect titrate to maintenance dose 100-450mg daily (2 divided doses). **Angina** – initiate with 50mg BID increase at weekly intervals to 100-400mg daily (2 divided doses). **Acute MI –** initiate with 3 IV boluses of 5 mg each at 2 minute intervals, 15 minutes after the final IV dose, initiate oral therapy with 50mg Q6H for 48 hours maintain with 100mg BID for up to 3 years (if unable to tolerate full IV dose, initiate oral with 25-50mg Q6H x 48 hour – maintain with 100mg BID up to 3 years) If unable to initiate immediately following MI may dose at 100mg BID up to 3 years.
FDA labeled Indications	▪ Hypertension ▪ Angina Pectoris	▪ Hypertension ▪ Angina Pectoris ▪ Myocardial Infarction ▪ Toprol XL: HTN, angina, CHF
Other studied uses	Congestive Heart Failure: initiate with 1.25mg daily, titrate to maximum of 10mg daily. Supraventricular arrhythmias, PVC's Angina Pectoris: 5-20mg daily Bisoprolol is approved for use in CHF in most European countries and Australia	▪ Immediate release: CHF (initiate with 6.25mg daily titrate gradually over 4-6 weeks to 50mg BID), Ventricular Arrhythmias (25-100mg daily), Atrial Ectopy, Migraine Prophylaxis (50-200mg daily),Essential Tremor, Aggressive Behavior, Antipsychotic Induced Akathisia, anxiety, hypertrophic cardiomyopathy, mitral valve prolapse, adjunct therapy for pheochromocytoma, thyrotoxicosis ▪ Toprol XL: Atrial Fibrillation/Flutter – 50-200mg daily

Beta Blockers (ß$_1$ selective)

Characteristic	Zebeta, Ziac (bisoprolol)	Lopressor, Toprol XL, Lopressor HCT (metoprolol)
Contraindications	Sinus bradycardia; greater than first-degree heart block; cardiogenic shock; CHF unless secondary to a tachyarrhythmia treatable with beta-blockers; overt cardiac failure; hypersensitivity to b-blocking agents. ▪ Acebutolol, carteolol: Persistently severe bradycardia. ▪ Propranolol, nadolol, timolol, penbutolol, carteolol, sotalol, and pindolol: Bronchial asthma, including severe chronic obstructive pulmonary disease. ▪ Metoprolol: Treatment of MI in patients with a heart rate < 45 BPM; significant heart block greater than first-degree (PR interval = 0.24 sec); systolic blood pressure < 100 mmHg; moderate to severe cardiac failure. ▪ Sotalol: Congenital or acquired long QT syndromes.	
Drug interactions	Beta Blocker Class – Aluminum salts, Barbiturates, Calcium salts, Cholestyramine, Colestipol, penicillins, Rifampin, Calcium Channel Blockers, oral contraceptives, flecainide, diphenhydramine, hydroxychloroquine, NSAID's, quinidine, ciprofloxacin, clinidine, disopyramide, epinephrine, ergot alkaloids, lidocaine, nondepolarizindg muscle relaxants, prazosin, sulfonylureas Non-Selective Beta Blockers – theophylline Metoprolol, Propranolol – cimetidine, hydralazine, propafenone, SSRI's, thioamines, Thyroid hormones, benzodiazepines Propranolol – haloperidol, loop diuretics, phenothiazines, anticoagulants, gabapentin Metoprolol, Nadolol – MAO inhibitors	
Major AEs / Warnings	Adverse effects are typically physiologic consequences of antagonized beta receptors in various tissues. Most adverse effects are mild and transient and rarely require withdrawal of therapy. ▪ Bradycardia, slowed A-V conduction, exacerbation bronchospasm in asthma or COPD, Raynaud's phenomenon, intermittent claudication, sexual dysfunction ▪ All ß-blockers have the potential to mask some of the manifestations of hypoglycemia, particularly tachycardia ▪ All ß-blockers should not be discontinued abruptly so as to avoid rebound hypertension; but, should be gradually tapered if drug is to be discontinued	
Dosage adjustment in key populations	Renal impairment - reduce dose if CrCl<40 ml/min - initiate with 2.5mg daily to maximum recommended dose 10mg daily Hepatic impairment: initiate with 2.5mg daily with maximum recommended dose 10mg. Elderly – initiate therapy with 2.5mg	Hepatic impairment – titrate slowly

Beta Blockers (β_1 selective)		
Characteristic	**Zebeta, Ziac (bisoprolol)**	**Lopressor, Toprol XL, Lopressor HCT (metoprolol)**
Pipeline Agents	▪ Nebivolol (no brand name, Bertek): Unlike other currently marketed beta blockers, nebivolol combines a high degree of beta$_1$ selectivity with nitric oxide – dependent vasodilation. This dual mechanism of action is considered unique to the compound. Nebivolol is currently marketed in 30 countries throughout Europe and Central America ▪ Celiprolol (no brand name): is a cardioselective beta-adrenergic blocking agent with alpha-2 receptor blocking activity and partial beta- 2 agonist vasodilatory properties. Celiprolol has been studied in heart failure and hypertension.	
Advantages/Unique Features	▪ Bisoprolol is approved for use in CHF in most European countries and Australia ▪ Bisoprolol was one of the first beta-blockers to exhibit outcomes data to support a mortality reduction in congestive heart failure (CIBIS II), which subsequently lead the way for other beta-blockers to be studied.	Metoprolol has shown improved post-infarction survival – decreasing the incidence of nonfatal cardiac arrest and cardiac death as well as reducing all-cause mortality. Metoprolol has exhibited outcomes data to support a mortality reduction in congestive heart failure..
Summary/Efficacy	▪ *See last page*	

Beta Blockers ($ß_1$ $ß_2$)				
Characteristic	**Cartrol (carteolol)**	**Corgard (nadolol) Corzide (plus HCTZ)**	**Levatol (penbutolol)**	**Visken (pindolol)**
Pharmacology	Carteolol is a nonselective ß-adrenergic receptor blocker with moderate intrinsic sympathomimetic activity and no membrane stabilizing activity.	Nadolol is a nonselective ß-adrenergic receptor blocker without membrane stabilizing or intrinsic sympathomimetic activity.	Penbutolol is a nonselective ß-adrenergic receptor blocker with low partial intrinsic sympathomimetic activity and no membrane stabilizing activity.	Pindolol is a nonselective ß-adrenergic receptor blocker with high intrinsic sympathomimetic activity and no membrane stabilizing activity.
	Beta-blockers are effective in the treatment of angina because they decrease heart rate, blood pressure, contractile force, and cardiac work load which reduces myocardial oxygen consumption, enhances coronary artery blood flow and improves myocardial perfusion. The antihypertensive mechanism of beta-blockers may be related to decreased cardiac output, reduced adrenergic energy, and inhibition of renin release. Beta-blockers exert an antiarrhythmic effect through inhibition of adrenergic stimulation of cardiac pacemaker potentials and slowing conduction through the atrioventricular node. Some supraventricular arrhythmias respond well to beta-blockers because they depress sinus node automaticity and suppress atrioventricular nodal conduction. The MSA (membrane stabilizing activity) may account for the antiarrhythmic activity by depressing excitability, prolonging refractory period and delaying conduction. Beta-blockers with intrinsic ISA offer advantage over other agents by reducing systemic blood pressure and total peripheral resistance without inducing important changes in heart rate, cardiac output, and renal blood flow.			
Manufacturer	Abbott	Corgard: available generically Corzide – Monarch	Schwarz Pharma	Available generically
FDA Approval Date	12/28/88	Off patent	1/5/89	Off patent
Generic formulation available?	No	Yes No-Corzide	No	Yes
Dosage forms / route of admin.	Tablets 2.5, 5 mg	Tablets 20, 40, 80, 120, 160 mg Corzide – 40/5, 80/5	Tablets 20 mg	Tablets 5, 10 mg
Dosing frequency	QD	QD	QD	BID

Beta Blockers (ß1 ß2)				
Characteristic	**Cartrol (carteolol)**	**Corgard (nadolol) Corzide (plus HCTZ)**	**Levatol (penbutolol)**	**Visken (pindolol)**
Generalized Dosing Guidelines	▪ Hypertension – initiate with 2.5mg daily and titrate to normal maintenance dose of 2.5-5mg QD. Maximum recommended dose – 10mg. Doses > 10mg may exhibit decreased effect.	▪ Angina, Hypertension – initiate with 40mg daily, increase by 40-80mg increments at 3-7 day intervals. ▪ Usual maintenance dose: Angina – 160-240mg daily Hypertension – 240-320mg daily	▪ Hypertension – initiate with 20mg daily. Full antihypertensive effect is seen at the end of a 2 week period. Doses as high as 40-80mg daily have been well tolerated, but little evidence of benefit at doses above 20mg	▪ Hypertension – initiate with 5mg BID, increase by 10mg/day every 3 to 4 weeks to maximum dose 60mg/day.
Pediatric Labeling	Safety and efficacy has not been established in children.	Safety and efficacy has not been established in children. Antiarrhythimia - 0.5-1mg/kg/dose q 12H, increase by 1mg/kg/day at 3-4 day intervals. Maximum of 2.5mg/kg/day.	Safety and efficacy has not been established in children.	Safety and efficacy has not been established in children.
FDA labeled Indications	Hypertension	▪ Hypertension ▪ Angina Pectoris	Hypertension	Hypertension

Beta Blockers ($ß_1$ $ß_2$)				
Characteristic	**Cartrol (carteolol)**	**Corgard, (nadolol) Corzide (with HCTZ)**	**Levatol (penbutolol)**	**Visken (pindolol)**
Other studied uses	Angina Pectoris	Ventricular Arrhythmias, Migraine Prophylaxis, Essential Tremor, Lithium-induced tremors, Parkinsonism Tremors, Aggressive Behavior, Anxiety, Antipsychotic Induced Akathisia, Esophageal Varices Rebleeding, hypertrophic cardiomyopathy, mitral valve prolapse, myocardial reinfarction prevention, portal hypertension, thyrotoxicosis	Angina Pectoris	Ventricular Arrhythmia/tachycardia (2.5-10mg Q6H), Antipsychotic Induced Akathisia, Anxiety, Angina Pectoris (10-40mg/day in divided doses), Augment for Antidepressant Therapy (2.5mg TID), Behavioral Disorder Associated with Dementia
Major AEs / Warnings	Adverse effects are typically physiologic consequences of antagonized beta receptors in various tissues. Most adverse effects are mild and transient and rarely require withdrawal of therapy. ▪ Bradycardia, slowed A-V conduction, exacerbation bronchospasm in asthma or COPD, Raynaud's phenomenon, intermittent claudication, sexual dysfunction ▪ All ß-blockers have the potential to mask some of the manifestations of hypoglycemia, particularly tachycardia ▪ All ß-blockers should not be discontinued abruptly so as to avoid rebound hypertension; but, should be gradually tapered if drug is to be discontinued			
Contraindications	Sinus bradycardia; greater than first-degree heart block; cardiogenic shock; CHF unless secondary to a tachyarrhythmia treatable with beta-blockers; overt cardiac failure; acute asthma; hypersensitivity to b-blocking agents. ▪ Acebutolol, carteolol: Persistently severe bradycardia. ▪ Propranolol, nadolol, timolol, penbutolol, carteolol, sotalol, and pindolol: Bronchial asthma, including severe chronic obstructive pulmonary disease. ▪ Metoprolol: Treatment of MI in patients with a heart rate < 45 BPM; significant heart block greater than first-degree (PR interval = 0.24 sec); systolic blood pressure < 100 mmHg; moderate to severe cardiac failure. ▪ Sotalol: Congenital or acquired long QT syndromes.			
Drug interactions	Beta Blocker Class – Aluminum salts, Barbiturates, Calcium salts, Cholestyramine, Colestipol, penicillins, Rifampin, Calcium Channel Blockers, oral contraceptives, flecainide, diphenhydramine, hydroxychloroquine, NSAID's, quinidine, ciprofloxacin, clinidine, disopyramide, epinephrine, ergot alkaloids, lidocaine, nondepolarizindg muscle relaxants, prazosin, sulfonylureas Non-Selective Beta Blockers – theophylline Metoprolol, Propranolol – cimetidine, hydralazine, propafenone, SSRI's, thioamines, Thyroid hormones, benzodiazepines Propranolol – haloperidol, loop diuretics, phenothiazines, anticoagulants, gabapentin Metoprolol, Nadolol – MAO inhibitors			

Beta Blockers ($ß_1$ $ß_2$)				
Characteristic	**Cartrol (carteolol)**	**Corgard, Corzide (nadolol)**	**Levatol (penbutolol)**	**Visken (pindolol)**
Dosage adjustment in key populations	Increase dosing interval in renal impairment CrCl 20-60ml/min q 48 h CrCl < 20ml/min q 72 h	Increase dosing interval in renal impairment CrCl 31-40ml/min q 24-36h or 50% normal dose CrCl 10-30ml/min q 24-48h or 50% normal dose CrCl < 10ml/min q 40-60h or 25% of normal dsoe May need to decrease dose with hepatic impairment Elderly – initiate with 20mg, increase by 20mg q 3-7 days, dosage range 20-240mg daily		Elderly – initiate with 5mg daily, increase by 5mg daily q 3-4 weeks. Decrease dose with severe hepatic or renal impairment.
Pipeline Agents	▪ Nebivolol (no brand name, Bertek): Unlike other currently marketed beta blockers, nebivolol combines a high degree of $beta_1$ selectivity with nitric oxide – dependent vasodilation. This dual mechanism of action is considered unique to the compound. Nebivolol is currently marketed in 30 countries throughout Europe and Central America ▪ Celiprolol (no brand name): is a cardioselective beta-adrenergic blocking agent with alpha-2 receptor blocking activity and partial beta- 2 agonist vasodilatory properties. Celiprolol has been studied in heart failure and hypertension.			
Advantages/Unique Features	Beta-blockers with intrinsic sympathomimetic activity may provide a diminished anti-hypertensive response due to a less pronounced decrease in cardiac output and do NOT impart benefit in migraine prophylaxis or post-MI.		Beta-blockers with intrinsic sympathomimetic activity may provide a diminished antihypertensive response due to a less pronounced decrease in cardiac output and do NOT impart benefit in migraine prophylaxis or post-MI.	Beta-blockers with intrinsic sympathomimetic activity may provide a diminished antihypertensive response due to a less pronounced decrease in cardiac output and do NOT impart benefit in migraine prophylaxis or post-MI.
Summary/Efficacy	*See last page of Class Review*			

Beta Blockers (ß$_1$ ß$_2$)			
Characteristic	**Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)**	**Betapace, Betapace AF (sotalol)**	**Blocadren (timolol) Timolide (with HCTZ)**
Pharmacology	Propranolol is a nonselective ß-adrenergic receptor blocker with membrane stabilizing activity and no intrinsic sympathomimetic activity.	Sotalol is a nonselective ß-adrenergic receptor blocker without intrinsic sympathomimetic activity or membrane stabilizing activity. In addition to class II beta-adrenergic antiarrhythmic effects, sotalol exerts class III antiarrhythmic effects, lengthening the action potential duration and prolonging the QTc interval on the electrocardiogram. The class II effects appear to contribute substantially to the superior mortality reduction with sotalol over class I agents, but the class III effects contribute to sotalol's antiarrhythmic efficacy in the treatment of ventricular tachyarrhythmias. Sotalol prolongs atrial and ventricular repolarization which is associated with an increase in the effective refractory period of cardiac tissues. Sotalol does not appear to affect atrial, His-Purkinje, or ventricular conduction velocity. The class III effects are due to potassium channel antagonism.	Timolol is a nonselective ß-adrenergic receptor blocker without membrane stabilizing activity or intrinsic sympathomimetic activity.
	Beta-blockers are effective in the treatment of angina because they decrease heart rate, blood pressure, contractile force, and cardiac work load which reduces myocardial oxygen consumption, enhances coronary artery blood flow and improves myocardial perfusion. The antihypertensive mechanism of beta-blockers may be related to decreased cardiac output, reduced adrenergic energy, and inhibition of renin release. Beta-blockers exert an antiarrhythmic effect through inhibition of adrenergic stimulation of cardiac pacemaker potentials and slowing conduction through the atrioventricular node. Some supraventricular arrhythmias respond well to beta-blockers because they depress sinus node automaticity and suppress atrioventricular nodal conduction. The MSA (membrane stabilizing activity) may account for the antiarrhythmic activity by depressing excitability, prolonging refractory period and delaying conduction. Beta-blockers with intrinsic ISA offer advantage over other agents by reducing systemic blood pressure and total peripheral resistance without inducing important changes in heart rate, cardiac output, and renal blood flow.		
Manufacturer	Innopran XL – Reliant Pharm Other formulations available generically	Betapace AF – Berlex Betapace: availabe generically	Blocadren available generically Timolide – Merck
FDA Approval Date	Innopran XL: March 12, 2003 Other formulations off patent	Betapace AF – Feb 22, 2000 (Expires 8/22/2003) Betapace: off patent	Blocadren: off patent Timolide – off patent – no generics
Generic available?	Inderal :Yes Innopran XL - No	Yes-Betapace, No-Betapace AF	Yes- Blocadren No – Timolide

Beta Blockers ($ß_1$ $ß_2$)			
Characteristic	**Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)**	**Betapace, Betapace AF (sotalol)**	**Blocadren (timolol) Timolide (with HCTZ)**
Dosage forms / route of admin.	▪ Tablets 10, 20, 40, 60, 80, 90mg (IR) ▪ Capsules 60, 80, 120, 160 mg (LA,ER) ▪ Solution, oral: 4 mg/mL, 8 mg/mL ▪ Oral solution, concentrated: 80 mg/mL ▪ Inderide – 40/25, 80/25mg ▪ Innopran XL – 80, 120mg	▪ Betapace and Generic Tablets 80, 120, 160, 240 mg ▪ Betapace AF-80, 120, 160 mg	▪ Tablets 5, 10, 20 mg ▪ Timolide – 10/25mg
Dosing frequency	IR: BID, TID, QI QD, Extended release preps: QD- BID	BID	BID

Beta Blockers (ß$_1$ ß$_2$)

Characteristic	Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)	Betapace, Betapace AF (sotalol)	Blocadren (timolol) Timolide (with HCTZ)
Generalized Dosing Guidelines	Tachyarrhythmias – 10-30mg q6-8h **Hypertension – initiate with 40mg BID, increase every 3-7 days to maintenance dose = 320mg (2-3 divided doses). Maximum recommended dose – 640mg** Migraine – initiate with 80mg/day (divided q6-8h), increase by 20-40mg q 3-4 weeks to maintenance of 160-240mg daily (divided q6-8h). If no satisfactory response within 6 weeks, gradually taper and discontinue LA – initiate with 80mg QD, titrate to 160-240mg QD Thyrotoxicosis – (Adult and Adolescents) 10-40mg q6h Akathisia – 30-120mg daily (3 divided doses)	▪ Sotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment. Proarrhythmic events can occur after initiation of therapy and with each upward dosage adjustment. ▪ Ventricular arrhythmias – initiate with 80mg BID, increase gradually to 240-320mg/day. Allow 3 days between dosing increments to attain steady state plasma concentration and to allow monitoring of QT interval. Most patients respond to doses of 160-320mg daily (2-3 divided doses). Some patients with life threatening refractory ventricular arrhythmias may require doses as high as 480-640mg daily only if benefit outweighs risk. ▪ Atrial fibrillation/flutter – initiate with 80mg BID. If the initial dose does not decrease the frequency of relapses of atrial fibrillation/flutter and is tolerated without excessive QT prolongation (not > 520msec) after 3 days, the dose may be increased to 120mg BID, may further increase dose to 160mg BID if response is inadequate and QT prolongation is not excessive.	▪ Hypertension – initiate with 10mg BID, increase every 7 days to usual maintenance dose of 20-40mg daily (in 2 divided doses). Maximum recommended dose 60mg daily. ▪ Prevention of myocardial reinfarction – 10mg BID – initiate within 1-4 weeks of infarct ▪ Migraine – initiate with 10mg BID, increase to maximum of 30mg daily.
Pediatric Labeling	▪ Tachyarrhythmias – initiate with 0.5-1mg/kg/day (divided q6-8h), titrate q 3-7 days to usual dose 2-4mg/kg/day to max recommended 16mg/kg/day or 60mg ▪ Hypertension – initiate with 0.5-1mg/kg/day (divided q6-12h), titrate q 3-7 days to maximum 2mg/kg/24 hours ▪ Migraines – 0.6-1.5mg/kg/day or = 35kg 10-20mg TID, >35kg 20-40mg TID ▪ Tetralogy spells – 1-2mg/kg/day (q6h prn) may increase by 1mg/kg/day to maximum of 5mg/kg/day. If refractory may gradually increase to 10-15mg/kg/day.	Safety and efficacy not established in children. Sotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment. Proarrhythmic events can occur after initiation of therapy and with each upward dosage adjustment. Dosing per manufacturer, based on pediatric pharmacokinetic data; wait at least 36 hours between dosage adjustments to allow monitoring of QT intervals. = 2 years: Dosage should be adjusted (decreased) by plotting of the child's age on a logarithmic scale. = 2 years: Initial: 90mg/m^2/day in 3 divided doses; may be incrementally increased to a maximum of 180mg/m^2/day	

Beta Blockers ($ß_1$ $ß_2$)			
Characteristic	**Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)**	**Betapace, Betapace AF (sotalol)**	**Blocadren (timolol) Timolide (with HCTZ)**
FDA labeled Indications	▪ Cardiac Arrhythmias ▪ Myocardial Infarction (reinfarct prevention) ▪ Hypertrophic subaortic stenosis ▪ Pheochromocytoma ▪ Hypertension ▪ Angina Pectoris ▪ Essential Tremor ▪ Migraine Prophylaxis ▪ Hyopertrophic cardiomyopathy	▪ Betapace: Ventricular Arrhythmias ▪ Betapace AF: Atrial fibrillation/flutter (AF) Manufacturer states substitution should not be made for AF since AF is distributed with patient package insert specific for Atrial fibrillation/flutter (this patient package insert and blue dye are the only differences between Betapace and Betapace AF).	▪ Hypertension ▪ Migraine prophylaxis ▪ Myocardial Infarction (reinfarct prevention)
Other studied uses	Parkinsonism Tremors, Alcohol Withdrawal, Aggressive Behavior, Anti-psychotic Induced Akathisia, Esophageal Varices Rebleeding, Anxiety, Gastric Bleeding in Portal Hypertension, Thyrotoxicosis, Schizophrenia/Acute Panic, mitral valve prolapse	Betapace: Atrial fibrillation/flutter Chronic angina, Hypertension Betapace AF: Atrial fibrillation/flutter Chronic angina, Hypertension	Ventricular Arrhythmias, Essential Tremor, Anxiety Angina, Mitral valve prolapse, Hypertrophic cardiomyopathy
Major AEs / Warnings	Adverse effects are typically physiologic consequences of antagonized beta receptors in various tissues. Most adverse effects are mild and transient and rarely require withdrawal of therapy. ▪ Bradycardia, slowed A-V conduction, exacerbation bronchospasm in asthma or COPD, Raynaud's phenomenon, intermittent claudication, sexual dysfunction ▪ All ß-blockers have the potential to mask some of the manifestations of hypoglycemia, particularly tachycardia ▪ All ß-blockers should not be discontinued abruptly so as to avoid rebound hypertension; but, should be gradually tapered if drug is to be discontinued		
Contraindications	Sinus bradycardia; greater than first-degree heart block; cardiogenic shock; CHF unless secondary to a tachyarrhythmia treatable with beta-blockers; overt cardiac failure; hypersensitivity to b-blocking agents. ▪ Acebutolol, carteolol: Persistently severe bradycardia. ▪ Propranolol, nadolol, timolol, penbutolol, carteolol, sotalol, and pindolol: Bronchial asthma, including severe chronic obstructive pulmonary disease. ▪ Metoprolol: Treatment of MI in patients with a heart rate < 45 BPM; significant heart block greater than first-degree (PR interval = 0.24 sec); systolic blood pressure < 100 mmHg; moderate to severe cardiac failure. ▪ Sotalol: Congenital or acquired long QT syndromes.		

Beta Blockers ($ß_1$ $ß_2$)			
Characteristic	**Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)**	**Betapace, Betapace AF (sotalol)**	**Blocadren (timolol) Timolide (with HCTZ)**
Drug interactions	Beta Blocker Class – Aluminum salts, Barbiturates, Calcium salts, Cholestyramine, Colestipol, penicillins, Rifampin, Calcium Channel Blockers, oral contraceptives, flecainide, diphenhydramine, hydroxychloroquine, NSAID's, quinidine, ciprofloxacin, clinidine, disopyramide, epinephrine, ergot alkaloids, lidocaine, nondepolarizindg muscle relaxants, prazosin, sulfonylureas Non-Selective Beta Blockers – theophylline Metoprolol, Propranolol – cimetidine, hydralazine, propafenone, SSRI's, thioamines, Thyroid hormones, benzodiazepines Propranolol – haloperidol, loop diuretics, phenothiazines, anticoagulants, gabapentin Metoprolol, Nadolol – MAO inhibitors		
Dosage adjustment in key populations	Marked slowing of heart rate may occur with cirrhosis with conventional doses; initiate with low dose and monitor heart rate regularly. Elderly – initiate with lower dose and titrate more slowly Renal Impairment CrCl 31-40ml/min dose q 24-36h or 50% normal dose CrCl 10-30ml/min dose q 24-48h or 50% normal dose CrCl < 10ml/min dose q 40-60h or 25% normal dose	Incr. dosing interval in renal impairment Betapace CrCl > 60ml/min dose q 12 hours CrCl 30-60ml/min dose q 24 hours CrCl 10-30ml/min dose q 36-48 hours CrCl <10ml/min individualize dose Betapace AF (A Fib/Flutter) CrCl > 60ml/min dose q 12 hours CrCl 40-60ml/min dose q 24 hours CrCl < 40ml/min med is contraindicated	
Pipeline Agents	▪ Nebivolol (no brand name, Bertek): Unlike other currently marketed beta blockers, nebivolol combines a high degree of $beta_1$ selectivity with nitric oxide – dependent vasodilation. This dual mechanism of action is considered unique to the compound. Nebivolol is currently marketed in 30 countries throughout Europe and Central America ▪ Celiprolol (no brand name): is a cardioselective beta-adrenergic blocking agent with alpha-2 receptor blocking activity and partial beta- 2 agonist vasodilatory properties. Celiprolol has been studied in heart failure and hypertension.		

Beta Blockers ($ß_1$ $ß_2$)			
Characteristic	**Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)**	**Betapace, Betapace AF (sotalol)**	**Blocadren (timolol) Timolide (with HCTZ)**
Unique Features/Advantages	Propranolol has shown improved post-infarction survival – decreasing the incidence of nonfatal cardiac arrest and cardiac death as well as reducing all-cause mortality. Propranolol has exhibited outcomes data to support a mortality reduction in congestive heart failure.	▪ Sotalol has the unique mechanism of action to reduce arrhythmias via both Class II (beta-blocking) and Class III (repolarization lengthening) activity. ▪ The only diferences between Betapace and Betapace AF are in the indications (Afib/Aflutter for Betapace AF and ventricular arrythmias for Betapace), tablet color, strengths available and the fact that Betapace AF must be distributed with a patient package insert (specific for Afib/Aflutter) whereas Betapace does not. ▪ Both contain the same active ingredients in the same release mechanism (just different dye/inert ingredients) ▪ Betapace has been used for Afib/Aflutter in clinical practice as a standard	Timolol has shown improved post-infarction survival – decreasing the incidence of nonfatal cardiac arrest and cardiac death as well as reducing all-cause mortality.

Beta Blockers ($ß_1$ $ß_2$)			
Characteristic	**Inderal, Inderal LA, Betachron ER, Innopran XL (propranolol)**	**Betapace, Betapace AF (sotalol)**	**Blocadren (timolol) Timolide (with HCTZ)**
Summary/Efficacy	▪ BBs with ISA may provide a diminished antihypertensive response due to a less pronounced decrease in heart rate and cardiac output. ▪ Nonselective beta-blockers (first generation) are not used in heart failure due to their poor tolerability ▪ To date, three beta-blockers have shown outcome benefits in heart failure trials, carvedilol, metoprolol, and bisoprolol. (Major trials of beta-blockers in congestive heart failure include are included in the following table on the next page). ▪ The COMET trial (Carvedilol or Metoprolol European Trial) in CHF has been highly criticized for the dosing of immediate release metoprolol (dose much lower in comparison to other trials of metoprolol in heart failure): **COMET**= Target dose of Metoprolol tartrate=2 x 50mg = 100mg Metoprolol tartrate **MERIT-HF**= Target dose of Metoprolol succinate (XR/CR)=1x 190mg succinate = 200mg Metoprolol tartrate ▪ It is worthy to note that both Coreg and labetalol have an $alpha_1$ adrenergic blocking component combined with their non-selective beta blockade. In March 2002, the fourth arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) sponsored by the NHLBI halted the arm containing the $alpha_1$ adrenergic blocker, Cardura ® (doxazosin). Data revealed that Cardura® was less effective than the more traditional diuretic in reducing some forms of cardiovascular disease, such as congestive heart failure and that users of the drug had a 25% more cardiovascular events and were twice as likely to be hospitalized for heart failure than users of the diuretic chlorthalidone. ▪ BBs with ISA do NOT impart benefit in migraine prophylaxis or post-MI. ▪ BBs without ISA are the only anti-arrhythmic agents that have improved post-infarction survival - decreasing the incidence of nonfatal cardiac arrest and cardiac death as well as reducing all-cause mortality. ▪ The benefits of BBs post-MI have been demonstrated with several agents: atenolol, metoprolol, timolol and propranolol (see following table). ▪ Differences between Betapace and Betapace AF are in indication, tablets strength and color, but not in active drug, mechanism of action or in release preparation.		

BETA-BLOCKERS IN CONGESTIVE HEART FAILURE

Study	**CIBIS-II [1,2]**	**MERIT-HF[3,4,5]**	**Packer, et al.[6]**	**Metra, et al[7]**
Study Design	Double-blind, multicenter, randomized, placebo-controlled	Double-blind, randomized, placebo-controlled	Double-blind, placebo-controlled, stratified	Double–blind, randomized
Population	▪ 2647 with stable NYHA class III or IV heart failure ▪ EF < 35% ▪ receiving standard therapy	▪ 3991 with stable NYHA class II-IV ▪ EF < 40% ▪ receiving standard therapy	▪ 1094 with stable NYHA class II-IV ▪ EF < 35% ▪ receiving standard therapy	▪ 150 with stable NYHA class II-IV ▪ EF < 35% ▪ receiving furosemide and an ACEI
Endpoints	Primary: all-cause mortality Secondary: hospitalization for worsening heart failure	Primary: total mortality; total mortality or all-cause hospitalizations Secondary: hospitalizations, NYHA class change, QOL	Mortality or hospitalization for cardiovascular reasons	Primary: LV EF Secondary: exercise tolerance, QOL, NYHA class, death, urgent transplantation
Treatment Regimen/ Duration	▪ Bisoprolol (n=1327) ▪ Placebo (n=1320) ▪ Mean follow-up: 1.3 years	▪ Metoprolol CR/XL (n=1990) ▪ Placebo (n=2001) ▪ Mean follow-up: 1 year	▪ Carvedilol (n=696) ▪ Placebo (n=398) ▪ Median duration of therapy 6.5 months	▪ Metoprolol BID (n=75) ▪ Carvedilol BID (n=75) ▪ Treatment duration: 23 + 12 months
Results	Bisoprolol vs Placebo ▪ All-cause mortality 11.8% vs 17.3% (p<0.0001) ▪ Sudden death: 55% risk reduction; 3.6% vs 6.3% (p=0.0011) ▪ Hospitalization due to CHF decreased 32% with bisoprolol (p<0.0001)	Metoprolol vs Placebo ▪ Sudden death: 55% risk reduction ▪ 19% risk reduction of all-cause mortality and hospitalizations (p<0.001) ▪ 31% RR of mortality and hospitalizations 2⌡CHF ▪ Decreased hospital days due to worsening HF (p<0.001)	Carvedilol vs Placebo ▪ Mortality: 65% risk reduction (p<0.001) ▪ Hospitalization for CV causes: 27% risk reduction (p<0.001) ▪ Mortality and hospitalization: 38% reduction (p<0.001)	▪ Carvedilol had greater increase in LV EF at rest (p=0.038) ▪ Carvedilol had greater decrease in mean pulmonary artery and wedge pressure (p<0.05) ▪ Metoprolol had greater increase in maximal exercise capacity (p=0.035) ▪ Death or urgent transplant C 17/75 vs M 21/75 ▪ Improved symptoms, QOL, & submaximal exercise tolerance were similar
Comments	▪ Study stopped early because of significant mortality benefit with bisoprolol	▪ Study stopped early because of significant mortality benefit with metoprolol CR/XL	▪ Study stopped early because of significant mortality benefit carvedilol	

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2. Dargie H. Recent clinical data regarding the use of beta blockers in heart failure: focus on CIBIS II. *Heart* 1999;82(Suppl 4):IV2-4.
3. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283(10):1295-1302
4. The International Steering Committee on Behalf of the MERIT-HF Study Group. Rationale, Design, and Organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). *Am J Cardiol* 1997;80(9B):54J-58J.
5. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure. *Lancet* 1999;353:2001-2007
6. Packer M, Bristow M, Cohn J, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996; 334: 1349-1355.
7. Metra M, Giubbini R, Nodari S, et al. Differential Effects of ß-Blockers in Patients with Heart Failure. *Circulation* 2000;102:546-551.

BETA BLOCKERS IN POST MYOCARDIAL INFARCTION

Study	ISIS-1[1]	TIMI II-B[2]	Norwegian Multicenter Study[3]
Study Design	Randomized, controlled, international trial	Multicenter, randomized, double blind, placebo-controlled	Multicenter, randomized, double-blind, placebo-controlled
Population	16,027	2,948 subjects who received IV TPA of which 1,434 were eligible for beta blocker therapy	1,884
Endpoints	Effect of short-term beta blocker therapy on mortality after MI	Effect of beta blocker therapy on mortality, reinfarction, and chest pain after MI following thrombolytic therapy	Effect of long-term Beta Blocker therapy on mortality and reinfarction after MI
Treatment Regimen/ Duration	▪ Atenolol 5-10 mg IV within a mean of 5 hours of chest pain, followed by 100 mg daily for 7 days (n=8,037)	▪ Immediate IV metoprolol 15 mg (5 mg every 5 minutes x 3), then 50 mg bid x 24 hours, then 100 mg bid x 42 days (n=720) ▪ 714 patients were deferred therapy and on day 6 received metoprolol 50 mg bid x 24 hours, followed by 100 mg bid thereafter for 6 weeks	▪ Timolol 10 mg bid 7-28 days after infarction and followed for 12-33 months (mean 17 months) (n=945)
Results	Atenolol vs Control ▪ Vascular mortality at follow up day 7: 3.89% vs 4.57% This 15% lower vascular mortality rate in the atenolol group was significant (2p<0.04)* ▪ Mortality for follow up days 7-365: 6.4% vs 7.0% (2p=0.09)* ▪ Vascular mortality for follow up days 0-365: 10.7% vs. 12.0% (2p<0.01)*	▪ Hospital mortality and 6 weeks mortality were similar between the 2 treatment groups ▪ Lower incidence of reinfarction (2.7% vs 5.1%, p=0.02) and recurrent chest pain (18.8% vs 24.1%, p<0.02) at 6 days in the immediate intravenous group	Timolol vs Placebo at 33 months ▪ Cumulated mortality: 10.6% vs 17.5%; timolol reduced mortality by 39.4% (p=0.0005) ▪ Sudden-death rate: 7.7% vs 13.9%; timolol reduced sudden death by 44.6% (p=0.0001) ▪ Cumulated reinfarction rate: 14.4% vs 20.1%; timolol reduced cumulated reinfarction by 28.4% (p=0.0006)

*Double-sided test of significance

1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group; Randomized Trial of Intravenous Atenolol Among 16,027 Cases of Suspected Acute Myocardial Infarction. Lancet 1986; 1:57-66.
2. Roberts R, Rogers WJ, Mueller HS, et al. Immediate Versus Deferred Beta Blockade Following Thrombolytic Therapy in Patients with Acute Myocardial Infarction; results of Thrombolysis in Myocardial Infarction (TIMI) II-B Study. Circulation 1991; 83:422-437.
3. Timolol-Induced Reduction in Mortality and Reinfarction in Patients Surviving Acute Myocardial Infarction; The Norwegian Multicenter Study Group. New England Journal of Medicine 1981; 304(14):801-807.

Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure.

Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O.
J Am Coll Cardiol. 2000 Jan;35(1):45-50.

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OBJECTIVES: To compare the hemodynamic effects of twice daily metoprolol tartrate (MT) and once daily metoprolol succinate (MS) in congestive heart failure patients. BACKGROUND: Adverse hemodynamic effects with MT demonstrated during initiation persist with drug readministration during chronic therapy. METHODS: Patients were randomly assigned to 6.25 mg MT or 25 mg MS orally and the dose was gradually increased to a target of 50 mg twice a day or 100 mg once a day, respectively. Hemodynamic measurements were obtained at baseline and after three months of therapy--both before and after drug readministration. RESULTS: Long term metoprolol therapy produced significant functional, exercise and hemodynamic benefits with no difference in response between either metoprolol preparation in the 27 patients (MT [14], MS [13]). When full dose metoprolol was readministered during chronic therapy, there were parallel adverse hemodynamic effects in both drug groups. Cardiac index decreased by 0.6 liters/min/m2 ($p < 0.0001$) with MT and by 0.5 liters/min/m2 ($p < 0.0001$) with MS. Systematic vascular resistance increased by 253 dyne-sec-cm(-5) ($p < 0.001$) with MT and by 267 dyne-sec-cm(-5) ($p < 0.0005$) with MS. Stroke volume index decreased by 7.0 ml/m2 ($p < 0.0005$) with MT and by 6.5 ml/m2 ($p < 0.0001$) with MS, while SWI decreased by 6.2 g-m/m2 ($p < 0.0005$) with MT and by 6.0 g-m/m2 ($p < 0.001$) with MS. CONCLUSION: Metoprolol tartrate and MS produce similar hemodynamic and clinical effects acutely and chronically despite the fourfold greater starting dose of MS used in this study. A more rapid initiation with readily available starting doses of MS may offer distinct advantages compared with MT in treating chronic heart failure patients with beta-adrenergic blocking agents.

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

4S	**S**candinavian **s**imvastatin **s**urvival **s**tudy;
6C trial	**c**ooperative **c**olorectal **c**ancer **c**ombination **c**hemotherapy **c**linical;
AAASPS	**A**frican-**A**merican **a**ntiplatelet **s**troke **p**revention **s**tudy;
AASK	**A**frican-**A**merican **s**tudy of **k**idney disease and hypertension
ABC study	**A**ssociation of **B**lack **C**ardiologists study of hypertension;
ABCD	**a**lternans **b**efore **c**ardioverter-**d**efibrillator **a**ppropriate **b**lood pressure **c**ontrol in **d**iabetes
AbESTT	**ab**ciximab [ReoPro™] in **e**mergent **s**troke **t**reatment **t**rial
ACADEMIC	**a**zithromycin in **c**oronary **a**rtery **d**isease: **e**limination of **m**yocardial **i**nfection with **c**hlamydia
ACAS	**a**symptomatic **c**arotid **a**therosclerosis **s**tudy;
ACCENT	**A** **C**rohn's disease **c**linical trial **e**valuating infliximab in a **n**ew long-term **t**reatment regimen
ACCESS	**a**cute **c**andesartan **c**ilexetil **e**valuation in **s**troke **s**urvivors **a** **c**ase **c**ontrol **e**tiological **s**tudy of **s**arcoidosis
ACCORD	**ac**tion to **c**ontrol **c**ardi**o**vascular **r**isk in **d**iabetes
ACES	**A**velox™ **c**linical **e**xperience **s**tudy **a**zithromycin and **c**oronary **e**vents **s**tudy
ACME	**a**ngioplasty **c**ompared to **me**dicine
ACIP	**a**symptomatic **c**ardiac **i**schemia **p**ilot study
ACRE	**a**ppropriateness of **c**oronary **re**vascularization
ACST	**a**symptomatic **c**arotid **s**urgery **t**rial
ACT	**a**ngioplasty **c**ompliance **t**rial **a**ttacking **c**laudication with **t**iclopidine
ACTION	**a** **c**linical **t**rial **i**n **o**vert **n**ephropathy; **act**inomycin eluting stent **i**mproves **o**utcomes by reducing **n**eointimal hyperplasia **a** **c**oronary disease **t**rial **i**nvestigating **o**utcome with **n**ifedipine GITS
ACUTE	**a**nalysis of **c**oronary **u**ltrasound **t**hrombolysis **e**ndpoints in acute myocardial infarction; Angiosonics **a**ssessment of **c**ardioversion **u**tilizing **t**ransesophageal **e**chocardiography;
ADAM	**A**msterdam **d**uration of **a**ntiretroviral **m**edication study **a**neurysm **d**etection **a**nd **m**anagement study
ADAPT	**A**lzheimer's **d**isease **a**nti-inflammatory **p**revention **t**rial;
ADCS	**A**lzheimer's **d**isease **c**ooperative **s**tudy
ADEMEX	**ade**quacy of peritoneal dialysis in **Mex**ico; sponsor: Baxter Healthcare Corporation
ADEPT	**a**dvanced **e**lements of **p**acing **t**rial; sponsor: Medtronic
ADMIRAL	**a**bciximab before **d**irect angioplasty and stenting in **m**yocardial **i**nfarction **r**egarding **a**cute and **l**ong-term followup
ADMIT	**a**rterial **d**isease **m**ultiple **i**ntervention **t**rial
ADONIS	**a**spirin **d**ose **o**ptimized in **n**oncardioembolic **i**schemic **s**troke
ADOPT	**a** **d**iabetes **o**utcome **p**rogression **t**rial;
ADOPT-A	**a**trial **d**ynamic **o**verdrive **p**acing **t**rial-**A**
ADVANCE	**a** **d**osing evaluation of a **v**asopressin **an**tagonist in **C**HF patients undergoing **e**xercise
AEGIS	**a**lternativ**e** **g**raft **i**nvestigational **s**tudy;
AFCAPS	**A**ir **F**orce **c**oronary **a**therosclerosis **p**revention **s**tudy
AFFIRM	**a**trial **f**ibrilation **f**ollowup: **i**nvestigation of **r**hythm **m**anagement

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

AFIB	**a**trial **f**ibrillation **i**nvestigation with **b**idisomide
AGENT	**a**ngiogenic **gen**e **t**herapy
AGIS	**a**dvanced **g**laucoma **i**ntervention **s**tudy
A-HeFT	**A**frican-American **he**art **f**ailure **t**rial;
AIR	**a**erosolized **i**loprost **r**andomized placebo-controlled study; sponsor: Schering AG
AIST-ASH	**a**cute **i**schemic **s**troke **t**rial: oral **as**pirin vs intravenous **h**eparin on stroke progression
ALERT	**a**djunctive **L**amictal® in **e**pilepsy and **r**esponse to **t**reatment **a**ssessment of **Le**scol® in **r**enal **t**ransplantation
ALIVE	**a**denosine **l**idocaine **i**nfarct zone **v**iability **e**nhancement **a**miodarone versus **l**idocaine **i**n prehospital **v**entricular fibrillation **e**valuation; sponsor: Wyeth Pharmaceuticals **a**zimi**l**ide post**i**nfarct sur**v**ival **e**valuation;
ALLHAT	**a**ntihypertensive and **l**ipid-**l**owering treatment to prevent **h**eart **a**ttack **t**rial;
ALLIANCE	**a**ggressive **l**ipid **l**owe**i**ng to **a**lleviate **n**ew **c**ardiovascular **e**ndpoints
ALTS	**A**SCUS/ **L**SIL **t**riage **s**tudy [ASCUS - atypical squamous cells of undetermined significance; LSIL - low-grade squamous intraepithelial lesion]
AMAZE	**a m**ulticenter trial using **A**tacand®-Zestril®* versus **Z**estril to evaluate the **e**ffects on lowering blood pressure [*Atacand as add-on therapy with Zestril]
AMIGO	**A**C2993: diabetes **m**anagement for **i**mproving **g**lucose **o**utcomes; sponsor: Amylin Pharmaceuticals, Inc.
AMISTAD	**a**cute **m**yocardial **i**nfarction **st**udy of **ad**enosine;
APASS	**a**nti**p**hospholipid **a**ntibody **s**troke **s**tudy
APC	**a**denoma **p**revention with **c**elecoxib;
APOCARD	**Apo**mate™ imaging in **card**iac transplant patients
APRES	**a**ngiotensin-converting enzyme inhibition **p**ost **re**vascularization **s**tudy
ARCH	**a**miodarone **r**eduction in **c**oronary **h**eart
ARCHeR	**A**cculink™ for **r**evascularization of **c**arotids in **h**igh-**r**isk patients
AREDS	**a**ge-**r**elated **e**ye **d**isease **s**tudy
ARIC	**a**therosclerosis **r**isk **i**n **c**ommunities
ARMS	**A**PSAC **r**eocclusion **m**ulticenter **s**tudy
ARREST	**A**ngioRad™ **r**adiation for **rest**enosis;
ARTISTIC	**A**ngioRad™ **r**adiation **t**herapy for **i**n-**st**ent restenosis **i**ntra**c**oronary;
ASAP	**a**zimilide **s**upraventricular **a**rrhythmia **p**rogram;
ASCENT	**A**CS **s**tent **c**linical **e**quivalence in de **n**ovo lesions **t**rial
ASCOT	**A**nglo-**S**candinavian **c**ardiac **o**utcome **t**rial
ASPECT	**a**nticoagulants in the **s**econdary **p**revention of **e**vents in **c**oronary **t**hrombosis;
ASPEN	**a**torvastatin [Lipitor™] **s**tudy for the **p**revention of **e**ndpoints for patients with **N**IDDM
ASSENT	**as**sessment of the **s**afety and **e**fficacy of a **n**ew **t**hrombolytic [TNKase™];
ASTIS	**a**utologous **s**tem cell **t**ransplantation **i**nternational **s**cleroderma trial
ASTRID	**a**trial **s**ensing **tr**ial to prevent **i**nappropriate **d**etections
ASTRONAUT	**a**cid **s**uppression **t**rial: **r**anitidine [Zantac®] versus **o**meprazole [Prilosec®] for **N**SAID-**a**ssociated **u**lcer **t**reatment
ATAC	**A**rimidex (anastrozole), **t**amoxifen **a**nd **c**ombination therapy **A**rimidex (anastrozole) and **t**amoxifen **a**lone or in **c**ombination
ATBAT	**a**nticoagulant **t**herapy with **b**ivalirudin [Angiomax™] to **a**ssist in PCI 1st inning **t**rial (PCI in HIT/HITTS)

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

ATICH	**a**ntifibrinolytic **t**herapy in acute **i**ntra**c**erebral **h**emorrhage
ATLAS	**A**colysis during **t**reatment of **l**esions **a**ffecting **s**aphenous vein bypass grafts; Angiosonics' Acolysis System™ **a**ssessment of **t**reatment with **l**isinopril **a**nd **s**urvival;
ATLANTIC	**a**ngina **t**reatments – **l**asers **a**nd **n**ormal **t**herapies **i**n **c**omparison
ATLANTIS	**a**lteplase **t**hrombo**l**ysis for **a**cute **n**oninterventional **t**herapy in **i**schemic **s**troke
AT LAST	**a**ntiretroviral **t**rial **l**ooking **a**t **s**ex and **t**reatment
AtoZ	**A**ggrastat® to **Z**ocor® study; sponsor: Merck
ATRIA	**a**n**t**icoagulation and **r**isk factors **i**n **a**trial fibrillation
ATS	**a**mblyopia **t**reatment **s**tudy
ATTRACT	**a**nti-**T**NF **t**rial in **r**heumatoid **a**rthritis with **c**A2 **t**reatment; **a**nti-**T**NF **t**rial in **r**heumatoid **a**rthritis with **c**oncomitant **t**herapy
AVASIS	**a**spirin **v**ersus **a**nticoagulants in **s**ymptomatic **i**ntracranial **s**tenosis
AVERT	**a**rtificial **v**alve **e**ndocarditis **r**eduction **t**rial **a**torvastatin **v**ersus **r**evascularization **t**reatments
AVID	**a**ntiarrhythmics **v**ersus **i**mplantable **d**efibrillators
AWESOME	**a**ngina **w**ith **e**xtremely **s**erious **o**perative **m**ortality **e**valuation
AZACS	**az**ithromycin in **a**cute **c**oronary **s**yndromes
BARI BARI 2D	**b**ypass **a**ngioplasty **r**evascularization **i**nvestigation **b**ypass **a**ngioplasty **r**evascularization **i**nvestigation **2 d**iabetes;
BARS	**B**eaumont **a**lcohol **r**estenosis **s**tudy
BASC	**b**lood pressure in **a**cute **s**troke **c**ollaboration
BATMAN	Bio*divYsio*® **bat**i**m**astat SV stent versus balloon **an**gioplasty for the reduction of restenosis in small coronary arteries;
BCPT	**b**reast **c**ancer **p**revention **t**rial
BEAT	**b**ucindolol **e**valuation in **a**cute myocardial infarction **t**rial;
BECAIT	**be**zafibrate **c**oronary **a**therosclerosis **i**ntervention **t**rial
BELLES	**b**eyond **e**ndorsed **l**ipid **l**owering with EBCT **s**cannings
BENEFIT	**Be**taferon® [Betaseron® in U.S.] in **n**ewly **e**merging MS **f**or **i**nitial **t**reatment; information
BENESTENT	**Be**lgium **Ne**therlands **stent**
BERT	**b**eta **e**nergy **r**estenosis **t**rial;
BESMART	**be**Stent™ in **sm**all **art**eries
BEST	**b**eta-blocker **e**valuation of **s**urvival **t**rial;
BEST-ICD	**b**eta-blocker **e**valuation of **s**urvival **t**rial plus **ICD**
BETTER	**be**ta radiation **t**rial **t**o **e**liminate **r**estenosis;
BHACAS	**b**eating **h**eart **a**gainst **c**ardioplegic **a**rrest **s**tudies
BIP	**b**ezafibrate **i**nfarction **p**revention
BLIND-DATE	**blind**ed withdrawal of deprenyl in the **DAT**ATOP **e**xtension trial
BLOSS	**b**eta blocker **l**ength **o**f **s**tay **s**tudy
BPAV	**b**alloon **p**rophylaxis of **a**neurysmal **v**asospasm
BRAINS	**B**ayer **r**andomized **a**cute **i**schemia **n**europrotectant **s**tudy **b**iochemical **r**esearch **a**nd **in**formation **s**tudy
BRAVO	**b**eta **r**adiation for treatment of **a**rterio**v**enous graft **o**utflow; sponsor: Novoste Corporation [Corona™ system] **b**lockade of the GP IIb/IIIa **r**eceptor to **a**void **v**ascular **o**cclusion;
BREATHE-1	**b**osentan [Tracleer™]: **r**andomized trial of **e**ndothelin receptor **a**ntagonist **the**rapy

	for pulmonary hypertension
BRILLIANT	**b**atimastat (BB-94) anti**r**estenosis tr**ial** uti**liz**ing the Bio*divYsio*® loc**a**l drug delivery PC ste**nt**;
BRITE BRITE-SVG	beta radiation to reduce in-stent restenosis; beta radiation to reduce in-stent restenosis for **s**aphenous **v**ein bypass **g**rafts
CABERNET	**c**arotid **a**rtery revascularization using the **B**oston Scientific **E**PI Filte**r**Wire EX and the EndoTex **Ne**xSten**t**
CACHET	**c**omparison of **a**bciximab **c**omplications with **H**irulog® [Angiomax™ as of 1999] ischemic **e**vents **t**rial
CADILLAC	**c**ontrolled **a**bciximab [ReoPro™] and **d**evice **i**nvestigation to **l**ower **l**ate **a**ngioplasty **c**omplications
CAESAR	**C**anada, **A**ustralia, **E**urope, **S**outh **A**f**r**ica AIDS study;
CALM	**c**andesartan **a**nd **l**isinopril **m**icroalbuminuria study
CALM-PD	**c**omparison of the **a**gonist pramipexole vs. **l**evodopa on **m**otor complications in Parkinson **d**isease
CALYPSO	**c**ylexin as an **a**djunct to **ly**tic therapy to **p**revent **s**uper**o**xide reflow injury
CAMELOT	**c**omparison of **a**mlodipine versus **e**nalapril [Lipitor®] to **l**imit **o**ccurrences of **t**hrombosis
CAMEO	**c**erebral **a**neurysm **m**ulticenter **E**uropean **O**nyx™
CANDLE	**cand**esartan versus **l**osartan **e**fficacy comparison;
CAPARES	**c**oronary **a**ngio **p**lasty **a**mlodipine **re**stenosis **s**tudy
CAPRICORN	**ca**rvedilol **p**ost infa**r**ction surv**i**val **co**nt**r**ol in left ventricular dysfunctio**n**
CAPRIE	**c**lopidogrel versus **a**spirin in **p**atients at **r**isk of **i**schemic **e**vents;
CAPT	**c**omplications of **A**MD [age-related macular degeneration] **p**revention **t**rial
CAPTEN	captopril after thrombolysis trial;
CAPTIM	**c**omparison of **a**ngioplasty and **p**rehospital **t**hrombolysis **i**n acute **m**yocardial **i**nfarction
CAPTIN	**capt**opril before reperfusion in acute myocardial **in**farction **cap**topril plus **t**issue plasminogen activator following acute myocardial **in**farction
CAPTURE	**c**7E3 **a**nti**p**latelet **t**herapy in **u**nstable **r**efractory **a**ngina
CARDIA	**c**oronary **a**rtery **r**isk **d**evelopment **i**n young **a**dults
CARDS	**c**ollaborative **a**to**r**vastatin [Lipitor™]and **d**iabetes **s**tudy
CARE	**c**alcium **a**ntagonist in **re**perfusion; **c**holesterol **a**nd **r**ecurrent **e**vents; **c**arvedilol **a**therectomy **re**stenosis;
CARE-HD	**c**oenzyme Q_{10} **a**nd **r**emacemide: **e**valuation in **H**untington **d**isease
CARE-HF	**ca**rdiac **re**synchronization - **h**eart **f**ailure; European complement to U.S./Canada MIRACLE study
CARISA	**c**ombination **a**ssessment of **r**anolazine **i**n **s**table **a**ngina;
CARMEN	**c**arvedilol **A**CE inhibitors **r**emodelling **m**ild heart failure **e**valuatio**n**
CART	**C**anadian **a**ntioxidant **r**estenosis **t**rial
CASES	**C**anadian **a**ctivase for **s**troke **e**ffectiveness **s**tudy
CASH	**c**ardiac **a**rrest **s**tudy-**H**amburg
CAST	**c**ardiac **a**rrhythmia **s**uppression **t**rial;
CASTLE	**c**andesartan **a**mlodipine **s**tudy of **t**olerabi**l**ity and **e**fficacy
CAT	**C**hinese **A**CE inhibitor in acute myocardial infarction **t**rial **ca**rdiomyopathy **t**rial
CATAPULT	**c**isplatin **a**nd **t**irapazamine in subjects with **a**dvanced **p**reviously **u**ntreated non–small cell **l**ung **t**umors

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

CATIE	**c**linical **a**ntipsychotic **t**rials of **i**ntervention **e**ffectiveness;
CATS	**C**anadian **A**merican **t**iclopidine **s**tudy **c**aptopril **a**nd **t**hrombolysis **s**tudy
CAVATAS	**ca**rotid and **v**ertebral **a**rtery **t**ransluminal **a**ngioplasty **s**tudy
CBT-CD	**c**ognitive **b**ehavior **t**herapy for the **c**hronic **d**epressions;
CEDARS	**c**omprehensive **e**valuation of **d**efibrillators **a**nd **r**esuscitative **s**hock
CEOS	**c**ongenital **e**sotropia **o**bservational **s**tudy
CHAMP	**c**hildren's **H**IV and **A**IDS **m**odel **p**rogram **c**ombination c**h**emotherapy **a**nd **m**ortality **p**revention
CHAMPIONS	**c**ontrolled **h**igh-risk subjects **A**vonex™ **M**S **p**revention **i**n **o**ngoing **n**eurologic **s**urveillance
CHAMPS	**c**ontrolled **h**igh-risk subjects **A**vonex™ **M**S **p**revention **s**tudy
CHARM	**c**andesartan cilexitil [Atacand™] in **h**eart failure **a**ssessment of **r**eduction **m**ortality and morbidity
CHEESE	**c**omparative trial of **H**IV-infected patients **e**valuating **e**fficacy and **s**afety of saquinavir-**e**nhanced oral formulation and indinavir given as part of a triple drug therapy;
CHF-STAT	**c**ongestive **h**eart **f**ailure **s**urvival **t**rial of **a**ntiarrhythmic **t**herapy
CHRISTMAS	**c**arvedilol **h**ibernation **r**eversible **i**schemia **t**rial; **ma**rker of **s**uccess
CHS	**c**ardiovascular **h**ealth **s**tudy **C**harleston **h**eart **s**tudy **c**ommunity **h**ealth **s**tudy **C**ongenital **H**eart **S**urgeons Society study **c**oronary **h**eart **s**tudy
CIBIS	**c**ardiac **i**nsufficiency **bi**soprolol **s**tudy
CIDS	**C**anadian **i**mplantable **d**efibrillator **s**tudy; sponsor: Medtronic
CIGTS	**c**ollaborative **i**nitial **g**laucoma **t**reatment **s**tudy
CLASS	**c**elecoxib [Celebrex®] **l**ong-term **a**rthritis **s**afety **s**tudy **cl**omethiazole **a**cute **s**troke **s**tudy
CLASSICS	**cl**opidogrel [Plavix™] **as**pirin **s**tent **i**nternational **c**ooperative **s**tudy
CLASS-IHT	**cl**omethiazole **a**cute **s**troke **s**tudy in **i**schemic, **h**emorrhagic, and **t**PA treated stroke
CLEERE	**c**ollaborative **l**ongitudinal **e**valuation of **e**thnicity and **r**efractive **e**rror
COAST	heparin-**coa**ted **st**ents in small coronary arteries
COCAD	**c**ognitive **o**utcomes in **c**oronary **a**rtery **d**isease
COLA	carvedilol **o**pen **l**abel **a**ssessment
COMBINE	**co**mbining **m**edications and **b**ehavorial **in**t**e**rventions;
COMET	**c**arvedilol **o**r **m**etoprolol **E**uropean **t**rial
COMMA	**com**pliment inhibition in **m**yocardial infarction treated with percutaneous transluminal coronary **a**ngioplasty [evaluation of IV dosing regimens of h5G1.1-scFv]; sponsors: Procter & Gamble and Alexion Pharmaceuticals
COMPANION	**co**mparison of **m**edical therapy, **p**acing **an**d defibrillat**ion** in chronic heart failure; Guidant Corporation
COMPLY	**comp**liment inhibition in myocardial infarction treated with thrombo**ly**tics [evaluation of IV dosing regimens of h5G1.1-scFv]; sponsors: Procter & Gamble Pharmaceuticals and Alexion Pharmaceuticals
COMS	**c**ollaborative **o**cular **m**elanoma **s**tudy
CONVINCE	**c**ontrolled **on**set **v**erapamil **in**vestigation of **c**ardiovascular **e**ndpoints
COOL	**c**ardiovascular thrombolytic to **o**pen **o**ccluded **l**ines [t-PA]
COOL AID	**cool** ing for **a**cute **i**schemic brain **d**amage;

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

COOL MI	**cool** ing as an adjunctive therapy to percutaneous intervention in patients with acute **m**yocardial **i**nfarction;
COPERNICUS	**c**arvedil**o**l [Coreg®] **p**rosp**e**ctive **r**a**n**dom**i**zed **cu**mulative **s**urvival
COPPA	**c**linical **o**utcomes from the **p**revention of **p**ostoperative **a**rrhythmia
CORE	**c**ontinuing **o**utcomes **r**elevant to **E**vista™
COSS	**c**arotid **o**cclusion **s**urgery **s**tudy
COURAGE	**c**linical **o**utcomes **u**tilizing **r**evascularization and **ag**gressive drug **e**valuation;
COURT	a randomized trial of **co**ntrast media **u**tilization in high **r**isk P**T**CA
CRASH	**c**orticosteroid **r**andomization **a**fter **s**ignificant **h**ead injury
CREDO	**c**lopidogrel [Plavix™] for **r**eduction of **e**vents **d**uring **o**bservation
CREST	**c**arotid **r**evascularization **e**ndarterectomy vs **s**tenting **t**rial
CRUISE	**c**an **r**outine **u**ltrasound **i**nfluence **s**tent **e**xpansion
CURE	**c**lopidogrel in **u**nstable angina to prevent **r**ecurrent ischemic **e**vents
DAIS	**d**iabetes **a**therosclerosis **i**ntervention **s**tudy
DAISY	**d**iabetes **auto**i**mmunity **s**tudy in the **y**oung
DATATOP	**d**eprenyl **a**nd **t**ocopherol **a**ntioxidative **t**herapy of **p**arkinsonism
DAVID	**d**ual-chamber **a**nd **V**VI **i**mplantable **d**efibrillator; see
DEBATE	**D**oppler **e**ndpoints **b**alloon **a**ngioplasty **t**rial **E**urope;
DECOPI	la **de**sobstruction **co**ronaire en **p**ost-**i**nfarctus
DEFINITE	**defi**brillators **i**n **n**on**i**schemic cardiomyopathy **t**reatment **e**valuation
DEFUSE	**d**iffusion-weighted imaging **e**valuation **f**or **u**nderstanding **s**troke **e**valuation;
DESTINI-CFR	**D**oppler **e**ndpoints **st**enting **in**ternational **i**nvestigation - **c**oronary **f**low reserve;
DIADS	**d**epression **i**n **A**lzheimer **d**isease **s**tudy
DIAGNOSIS	**d**iffusion-weighted **i**maging **a**ssessment of the **g**enuine **n**eed for **o**ther **s**tudies in **i**schemic **s**troke
DIAMOND	**d**istensibility **i**mprovement with **A**LT-711 re**mo**deli**n**g in **d**iastolic heart failure; sponsor: Alteon Inc.
DIAMOND CHF	**D**anish investigators of **a**rrhythmia and **m**ortality **on d**ofetilde **c**ongestive **h**eart **f**ailure;
DIGAMI	**d**iabetes **m**ellitus **i**nsulin-**g**lucose infusion in **a**cute **m**yocardial **i**nfarction
DMIST	**d**igital **m**ammographic **i**maging **s**creening **t**rial
DINAMIT	**d**efibrillation **in a**cute **m**yocardial **i**nfarction **t**rial
DIRECT	**di**abetic **re**tinopathy **c**andesartan **t**rial; candesartan cilexetil (Atacand®)
DIRECTOR	**direct** stenting study with **Or**bus R stent™; sponsor: Orbus Medical Technologies
DISC	**d**isability **i**n **s**trategies for **c**are
DISTINCT	Bio**di**vYsio™ **st**ent **in** controlled **t**rial
DPT-1	**d**iabetes **p**revention **t**rial **-** type **1**;
DREAM	**d**iabetes **re**duction **a**pproaches with ramipril and rosiglitazone **m**edications
DYSBOT	**Dys**port and **Bot**ox study;
EAGAR	**e**strogen **a**nd **g**raft **a**therosclerosis **r**esearch trial
EARS	**E**uropean **a**therosclerosis **r**esearch **s**tudy
ECCO 2000	**e**ffects of **c**iticoline (CerAxon™) on **c**linical **o**utcome - **2000** mg;
EDGE™	**e**valuation of **d**aptomycin [Cidecin™] in **g**ram-positive **e**ntities
EDGE[CAP]	**e**valuation of **d**aptomycin [Cidecin™] in **g**ram-positive **e**ntities in the treatment of community-**a**cquired **p**neumonia
EDGE[SST]	**e**valuation of **d**aptomycin [Cidecin™] in **g**ram-positive **e**ntities in the treatment of complicated **s**kin and **s**oft **t**issue infections

EDGE^{UTI}	evaluation of daptomycin [Cidecin™] in gram-positive entities in the treatment of complicated urinary tract infection
ED-IMPACT	emergency department impedance cardiography-aided assessment changes therapy; sponsor: CardioDynamics International
EFICAT	ejection fraction in cardiac transplant patients
EGASIS	early GABA-ergic activation s</Bin troke
ELECT	evaluating enoxaparin [Lovenox®] clotting times; see
ELITE	evaluation of losartan in the elderly
ELLDOPA	earlier versus later levodopa in Parkinson disease
ENABLE	endothelin antagonist bosentan for lowering cardiac events in heart failure
ENCORE	evaluation of nifedipine and cerivastatin on the recovery of endothelial function; web site
ENRICHD	enhancing recovery in coronary heart disease
ENTIRE	enoxaparin and TNK-tPA with or without GP IIb/IIIa inhibitor as reperfusion strategy in ST elevation MI [TIMI-23];
EPHESUS	eplerenone neurohormonal efficacy and survival study; eplerenone post-AMI heart failure efficacy and survival study
EPIC	evaluation of c7E3 for prevention of ischemic complications
EPILOG	evaluation in PTCA to improve long-term outcome with abciximab GP IIb/IIIa blockade;
EPISTENT	evaluation of platelet IIb/IIIa inhibitor for stenting trial
ERA	early rheumatoid arthritis (RA) study enoxaparin restenosis after angioplasty study estrogen replacement and atherosclerosis study
ERASE	emergency room assessment of sestamibi for evaluation of chest pain
ERGO	etomoxir for the recovery of glucose oxidation
ER-TIMI	early Retavase™ - thrombolysis in myocardial infarction
ESCAPE	evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness
ESPRIT	enhanced suppression of the platelet IIb/IIIa receptor with Integrilin™ therapy European study of the prevention of reocclusion after initial thrombolysis evaluation of subcutaneous proleukin in a randomized international trial
ESPS2	European stroke prevention study 2
ESSENCE	efficacy and safety of subcutaneous enoxaparin in non–Q-wave coronary events;
ESSENTIAL	the studies of oral enoximone therapy in advanced heart failure; sponsor: Myogen, Inc.
ETHECC	evaluation of Thymitaq™ in hepatocellular carcinoma; sponsor: Eximas Pharmaceutical Corporation
ETROP	early treatment of retinopathy of prematurity
Euro-SPAH	European-sonotherapy prevention of arterial hyperplasia; sponsor: PharmaSonics, Inc.
EVIDENCE	evidence for interferon dose-effect: European-North American comparative efficacy study [Rebif® v. Avonex™ in relapsing-remitting multiple sclerosis (RRMS)]
EVIDENT	endovascular investigation determining the safety of a new tacrolimus-eluting stent graft; sponsor: JOMED N.V.
EXCITE	evaluation of oral xemilofiban in controlling thrombotic events;
EXCITe	extremity constraint-induced therapy
EXCLAIM	extended clinical prophylaxis in acutely ill medical patients [Lovenox™ (enoxaparin) postmarketing (phase IV) trial]; sponsor: Aventis

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

FACET	**f**osinopril versus **a**mlodipine **c**ardiovascular **e**vents randomized **t**rial
FAME	**f**luvastatin [Lescol®] **a**ssessment of **m**orbi-mortality in the **e**lderly
FASTER	**f**ibrinolytic and **A**ggrastat® **ST e**levation **r**esolution; **f**irst **a**barelix depot **s**tudy for **t**reating **e**ndometriosis **r**apidly **f**irst **a**nd **s**econd **t**rimester **e**valuation of **r**isk; see study information
FAST-MAG	**f**ield **a**dministration of **s**troke **t**herapy - **mag**nesium
FIELD	**f**enofibrate [TriCor®] **i**ntervention and **e**vent **l**owering in **d**iabetes
FIRST	**F**lolan (dobutamine) **i**nternational **r**andomized **s**urvival **t**rial **f**irst trimester **i**ntegrated **r**isk **s**creening for **t**risomy [information]
FLARE	**fl**uvastatin [Lescol®] **a**ngiographic **re**stenosis
FOOD	**f**eed **o**r **o**rdinary **d**iet
FOSIT	**Fos**amax® **i**nternational **t**rial
FRAXIS / FRAX.I.S.	**Frax**iparine® in **i**schemic **s**yndromes
FRIC	**Fr**agmin® **i**n unstable **c**oronary artery disease
FRISC	**f**ast **r**evascularization during **i**n**s**tability in **c**oronary artery disease **Fr**agmin® during **i**n**s**tability in **c**oronary artery disease
FROSTY	**Fr**eezor™ trial **o**f **s**upraventricular **t**ach**y**cardia
FUSION	**f**ractional flow reserve and **u**ltra**s**ound **i**ndices for **o**bjective **n**arrowing assessment
GART study	**g**enotypic **a**ntiretroviral **r**esistance **t**esting
GEMS	**G***inkgo biloba* **e**valuation **m**emory **s**tudy
GISEN	**g**ruppo **I**taliano di **s**tudi **e**pidemiologici in **n**efrologia
GUSTO	**g**lobal **u**tilization of **s**treptokinase and **t**PA for **o**ccluded arteries;
GUSTO-SPEED	**g**lobal **u**tilization of **s**treptokinase and **t**PA for **o**ccluded arteries–**s**trategies for **p**atency **e**nhancement in the **e**mergency **d**epartment
HALT-C	**h**epatitis C **a**ntiviral **l**ong-term **t**reatment to prevent **c**irrhosis;
HANDLS	**h**ealth **a**ging in **n**ationally **d**iverse **l**ongitudinal **s**amples
HARDBALL	**h**eart **a**llograft **r**ejection: **d**etection with **b**reath **a**lkanes in **l**ow **l**evels
HeADDFIRST	**he**micraniectomy **a**nd **d**urotomy for **d**eterioration **f**rom **i**nfarction **r**elating **s**welling **t**rial
HEART	**h**ealing and **e**arly **a**fterload **r**educing **t**herapy
HEAT 2	**h**ypertension **e**ndothelin **a**ntagonist **t**reatment
HEME	**h**emorrhage **e**arly **M**RI **e**valuation
HERO	**H**irulog® **e**arly **r**eperfusion/**o**cclusion trial
HERS	**h**eart and **e**strogen/progestin **r**eplacement **s**tudy **H**IV **e**pidemiology **r**esearch **s**tudy
HESTIA	**h**ome **e**valuation of **st**roke **i**nduced **a**id
HIPS	**h**eparin **i**nfusion **p**rior to **s**tenting;
HIT	**H**DL-cholesterol **i**ntervention **t**rial **h**irudin for the **i**mprovement of **t**hrombolysis
HOPE	**h**eart **o**utcomes **p**revention **e**valuation;
HOPE-TOO	**h**eart **o**utcomes **p**revention **e**valuation - **t**he **o**ngoing **o**utcomes
HORIZON	**h**ealth **o**utcomes and **r**educed **i**ncidence with **z**oledronic **on**ce yearly
HOT	**h**ypertension **o**ptimum **t**reatment
HPS	**h**eart **p**rotection **s**tudy
HRS	**h**ealth and **r**etirement **s**tudy
HYVET	**hy**pertension in the **v**ery **e**lderly **t**rial
ICE-IT	**i**ntravascular **c**ooling adjunctiv**e** to primary coronary **i**n**t**ervention
ICSS	**i**nternational **c**arotid **s**tenting **s**tudy (CAVATAS-2)

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

IDEAL	**i**ncremental **d**ecrease in **e**ndpoints through **a**ggressive **l**ipid lowering **I**ressa® **d**ose **e**valuation in **a**dvanced **l**ung cancer
IDNT	**i**rbesartan [Avapro®] in **d**iabetic **n**ephropathy **t**rial
IHAST	**i**ntraoperative **h**ypothermia for **a**neurysm **s**urgery **t**rial
IMAGES	**i**ntravenous **mag**nesium **e**fficacy in **s**troke
IMAGINE	**i**schemic **m**anagement with **A**ccupril™ post bypass **g**raft via **i**nhibition of co**n**verting **e**nzyme
IMPACT	**I**ntegrilin™ to **m**anage **p**latelet **a**ggregation to prevent **c**oronary **t**hrombosis **i**nternational **m**exiletine or **p**lacebo **a**ntiarrhythmic **c**oronary **t**rial; **i**nternational **m**ultiple sclerosis secondary progressive **A**vonex™ **c**ontrolled **t**rial
IMPRESS	**i**nhibition of **m**etallo **p**rotease by BMS-186716 in a **r**andomized **e**xercise and **s**ymptoms **s**tudy;
IMS	**i**nterventional **m**anagement of **s**troke study
INCOMIN	**in**dependent **com**parison of **in**terferon [Betaseron® v. Avonex™ in relapsing-remitting multiple sclerosis (RRMS)]
InDDEx	**in**vestigation into **d**elay to **d**iagnosis of Alzheimer disease with **Ex**elon™
INHIBIT	**in**timal **h**yperplasia **i**nhibition with **b**eta **i**n-stent **t**rial; Guidant Corporation
INSIGHT	**i**nternational **n**ifedipine once-daily **s**tudy – **i**ntervention as a **g**oal in **h**ypertension **t**reatment; web site
INTACT	**I**ressa® **n**on–small cell lung cancer **t**rial **a**ssessing **c**ombination **t**reatment
INTEGRITI	**Integri**lin® and **t**enecteplase [TNKase™] in acute myocardial **i**nfarction;
InTIME	**i**ntravenous **n**PA for **t**reatment of **i**nfarcting **m**yocardium **e**arly;
INTrEPID	**i**nvestigation of **n**on–**tr**ansplant-**e**ligible **p**atients who are **i**notrope **d**ependent; see
INTRO-AMI	**Int**egrilin® and **r**educed dose **o**f thrombolytic in **a**cute **m**yocardial **i**nfarction
IONA	**i**mpact **o**f **n**icorandil in **a**ngina
IONDT	**i**schemic **o**ptic **n**europathy **d**ecompression **t**rial
IRAS	**i**nsulin **r**esistance **a**therosclerosis **s**tudy
IRMA 2	**ir**besartan [Avapro®] **m**icro**a**lbuminuria type **2**
IRIS	**I**sostent for **r**estenosis **i**ntervention **s**tudy
ISAAC	**i**nternational **s**tudy of **a**sthma and **a**llergies in **c**hildhood
ISAR	**i**ntracoronary **s**tenting and **a**ntithrombotic **r**egimen
ISAR-STEREO	**i**ntracoronary **s**tenting and **a**ngiographic **r**esults - **s**trut **t**hickness **e**ffect on **re**stenosis **o**utcome
ISAT	**i**nternational **s**ubarachnoid **a**neurysm **t**rial
ISTICH	**i**nternational **s**urgical **t**rial in *i*ntra**c**erebral **h**emorrhage
ITT	**i**ntraventricular **t**hrombolysis **t**rial
IVAT	**i**ntermediate sized **v**essel **a**therectomy **t**rial
L-CAD	**l**ipid-**c**oronary **a**rtery **d**isease [pravastatin]; sponsor, Bristol-Myers Squibb
LACI	**l**aser **a**ngioplasty for **c**ritical **i**schemia;
LAMP	**l**ocally **a**dvanced **m**ultimodality **p**rotocol;
LARS	**l**aser **a**ngioplasty in **r**estenosed **s**tents
LaSRS	**la**te **s**teroid **r**escue **s**tudy
LATE	**l**ate **a**ssessment of **t**hrombolytic **e**fficacy;
LEADER	**l**ower **e**xtremity **a**rterial **d**isease **e**vent **r**eduction
LIDO	**l**evosimendan [Simdax™] **i**nfusion versus **do**butamine in low output heart failure
LIDS	**l**umbar **i**nvertebrae **d**isk **s**tudy [device trial]
LIFE	**l**osartan **i**ntervention **f**or **e**ndpoint reduction in hypertension
LIMB	ultrasound **l**ysing **i**n lower extremities to **m**inimize **b**lood clots; Angiosonics

LIMIT	**l**ong lesion **i**ntracoronary radiation to **m**inimize **i**ntimal hyperplasia **t**rial; sponsor: Guidant Corp. [Galileo™ intravascular radiotherapy system]
LIPID	**l**ong-term **i**ntervention with **p**ravastatin in **i**schemic **d**isease;
LONG WRIST	**W**ashington **r**adiation for **i**n-**s**tent restenosis **t**rial for **long** lesions
Look AHEAD	**a**ction for **hea**lth in **d**iabetes [Xenical; long-term study of effects of weight loss in type 2 diabetics]
L-TAP	**l**ipid **t**reatment **a**ssessment **p**roject
LV3P-CHF	**l**eft **v**entricular **p**acing in **p**acemaker **p**atients with **c**ongestive **h**eart **f**ailure (CHF); sponsored by St. Jude Medical
MADIT	**m**ulticenter **a**utomatic **d**efibrillator **i**mplantation **t**rial
MAGIC	**mag**nesium **i**n **c**oronay arteries
MARISA	**m**onotherapy **a**ssessment of **r**anolazine **i**n **s**table **a**ngina;
MARRVEL	**ma**gnetic **r**esonance **r**adionuclide **v**entriculography and **e**chocardiography in **l**eft ventricular function
MARVAL	**m**icro **a**lbuminuria **r**eduction with **val**sartan [Diovan®]
MASH	**m**agnesium and **a**cetylsalicylic acid in **s**ubarachnoid **h**emorrhage
MATCH	**m**anagement of **a**thero**t**hrombosis with **c**lopidogrel [Plavix™] in **h**igh-risk patients with recent transient ischemic attack or ischemic stroke
MDC	**m**etoprolol in **d**ilated **c**ardiomyopathy
MDPIT	**m**ulticenter **d**iltiazem **p**ost **i**nfarction **t**rial
MEDENOX	prophylaxis in **med**ical patients with **enox**aparin [Lovenox®]
MERIT-HF	**me**toprolol CR/XL (controlled release) **r**andomized **i**ntervention **t**rial in **h**eart **f**ailure;
MIAMI	**M**ulti-Link® Duet™ coronary stent **i**n **a**cute **m**yocardial **i**nfarction
MICRO-HOPE	**mi**croalbuminuria, **c**ardiovascular, and **r**enal **o**utcomes (HOPE [**h**eart **o**utcomes **p**revention **e**valuation] substudy)
MIRA	**m**inocycline **i**n **r**heumatoid **a**rthritis
MIRACL	**m**yocardial **i**schemia **r**eduction with **a**ggressive **c**holesterol **l**owering
MIRACLE	**m**ulticenter **I**nSync™ **ra**ndomized **cl**inical **e**valuation (North America)
MIRACLE ICD	**m**ulticenter **I**nSync™ **ra**ndomized **cl**inical **e**valuation **i**mplantable **c**ardioverter **d**efibrillator
MIRAGE	**m**ulti-**i**nstitutional **r**esearch in **A**lzheimer **g**enetic **e**pidemiology
MMAIT	**m**alignant **m**elanoma **a**ctive **i**mmunotherapy **t**rials; [Canvaxin™]
MMSS	**M**yoVive™ **m**arketing **s**urveillance **s**tudy;
MOBILE	**mo**re **p**atency with **b**eta for **i**n-stent restenosis in the **l**ower **e**xtremity; sponsor: Novoste Corporation [Corona™ system]
MOCHA	**m**ulticenter **o**ral **c**arvedilol [Coreg®] **h**eart **f**ailure **a**ssessment
MONICA	**moni**toring trends and determinants **i**n **ca**rdiovascular disease
MORE	**m**ultiple **o**utcomes of **r**aloxifene **e**valuation
MOST	**mo**de **s**election **t**rial in sinus node dysfunction
MOXCON	**mox**onidine **con**gestive heart failure trial;
MRFIT	**m**ultiple **r**isk **f**actor **i**ntervention **t**rial
MR IMAGES	**m**agnetic **r**esonance in **i**ntravenous **mag**nesium **e**fficacy in **s**troke
MSMI	**m**ulticenter **s**tudy of **m**yocardial **i**schemia
MUST	**m**edication **u**se **st**udies; **mu**lticenter **st**ent study; **mu**lticenter **s**tents **t**iclopidine;
MUST EECP	**mu**lticenter **st**udy of **e**nhanced **e**xternal **c**ounter**p**ulsation [EECP®]

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

MUSTIC	**mu**ltisite **st**imulation **i**n **c**ardiomyopathy
MUSTT	**m**ulticenter **u**n**s**table **t**achycardia **t**rial; **m**ulticenter **u**n**s**ustained **t**achycardia **t**rial;
NAFT	**N**orth **A**merican **F**ragmin® **t**rial
NASCET	**N**orth **A**merican **s**ymptomatic **c**arotid **e**ndarterectomy **t**rial;
NAVIGATOR	**n**ateglinide **a**nd **v**alsartan in **i**mpaired **g**lucose **t**olerance **o**utcomes **r**esearch;
NETT	**n**ational **e**mphysema **t**reatment **t**rial
NETWORK	**Network** of general practitioners and hospital physicians involved in the study of low versus high doses of enalapril in patients with heart failure trial
NICE	**N**ovacor® **i**nflow **c**onduit **e**valuation; sponsor: World Heart Corporation
NICE 3	**n**ational **i**nvestigators **c**ollaborating on **e**noxaparin [Lovenox®]
NOCIS	**n**ew **o**nset **C**rohn's **i**ntervention **s**tudy
OASIS / OASIS-2	**o**rganization to **a**ssess **s**trategies for **i**schemic **s**yndromes
OAT	**o**pen **a**rtery **t**rial
OBJECT	**o**veractive **b**ladder: **j**udging **e**ffective **c**ontrol and **t**reatment [Ditropan XL v. Detrol]
OCBAS	**o**ptimal **c**oronary **b**alloon **a**ngioplasty versus **s**tent
OCTAVE	**o**mapatrilat [Vanlev™] **c**ardiovascular **t**reatment **a**ssessment **v**ersus **e**nalapril
OHTS	**o**cular **h**ypertension **t**reatment **s**tudy
OMNIUM	**o**meprazole [Prilosec®] versus **m**isoprostol [Cytotec®] for **N**SAID-**i**nduced **u**lcer **m**anagement
ONTARGET	**on**going **t**elmisartan [Micardis®] **a**lone and in combination with **r**amipril [Altace®] **g**lobal **e**ndpoint **t**rial
OPERA	**o**mapatrilat [Vanlev™] in **p**ersons with **e**nhanced **r**isk of **a**therosclerotic events;
OPTIC	**o**ptimal **p**harmacological **t**herapy in **i**mplantable **c**ardioverter defibrillator patients; sponsor: St. Jude Medical
OPTIMAAL	**op**timal **t**rial **i**n **m**yocardial infarction with the **a**ngiotensin II **a**ntagonist **l**osartan
OPTIME-CHF	**o**utcomes of a **p**rospective **t**rial of **i**ntravenous **m**ilrinone for **e**xacerbations of **c**hronic **h**eart **f**ailure
OPUS	**o**rbofiban in **p**atients with **u**nstable coronary **s**yndromes
ORBIT	**o**ral glycoprotein IIb/IIIa **r**eceptor **b**lockade to **i**nhibit **t**hrombosis;
OVERTURE	**o**mapatrilat **v**ersus **e**nalapril **r**andomized **t**rial of **u**tility in **r**educing **e**vents;
PAC-A-TACH	**pac**ing in **a**trial fibrillation and **tach**ycardia
PACIFIC	**p**otential **a**ngina **c**lass **i**mprovement **f**or **i**ntramyocardial **c**hannels
PACT	**P**hiladelphia **A**ssociation of **C**linical **T**rials study **p**lasminogen activator **a**ngioplasty **c**ompatibility **t**rial **p**rehospital **a**pplication of **c**oronary **t**hrombolysis **p**rourokinase in **a**cute **c**oronary **t**hrombosis
PAMI	**p**rimary **a**ngioplasty in acute **m**yocardial **i**nfarction;
PARADIGM	**p**ramlintide for **a**mylin **r**eplacement **a**djunct for **d**iabetes **i**n **g**lycemic **m**anagement;
PARAGON	**p**latelet IIb/IIIa **a**ntagonism for the **r**eduction of **a**cute coronary syndrome events in the **g**lobal **o**rganization **n**etwork
PARIS	**p**eripheral **a**rtery **r**adiation **i**nvestigational **s**tudy [study of the Nucletron® Paris® leg artery radiation catheter]
PASS II	**p**iracetam **a**cute **s**troke **s**tudy II
PATH-CHF	**pa**cing **th**erapies for **c**ongestive **h**eart **f**ailure
PAVE	**p**ost **AV** node ablation **e**valuation; sponsored by St. Jude Medical
PCDD	**p**revention of **c**ardiovascular **d**isease in **d**iabetes
PCI-CURE	**c**lopidogrel [Plavix®] in **u**nstable angina to prevent **r**ecurrent ischemic **e**vents in

	patients undergoing **p**ercutaneous **c**oronary **i**ntervention; companion to CURE study
PCPT	**p**rostate **c**ancer **p**revention **t**rial; information
PDQUALIF	**P**arkinson('s) disease **qua**lity of **lif**e
PEACE	**p**revention of **e**vents with **a**ngiotensin **c**onverting **e**nzyme [ACE] inhibitor therapy
PEECH™	**p**rospective **e**valuation of **E**ECP® in **c**ongestive **h**eart failure; sponsor, Vasomedical, Inc.
PENTALYSE	synthetic **pent**asaccharide as an **a**djunct to fibrino**ly**sis in **S**T-**e**levation acute myocardial infarction
PENTUA	**p**entasaccharide in **u**nstable **a**ngina
PEPI	**p**ostmenopausal **e**strogen/**p**rogestin **i**nterventions study
PETHEMA	**p**rograma para el **e**studio y **t**ratamiento de las **he**mopatías **ma**lignas [program for the study and treatment of malignant hemopathies]
PHADE	**p**neumatic **H**eartMate® **a**ssist as **d**estination **e**valuation;
PHAROS	**p**ilot **H**untington **a**t **r**isk **o**bservational **s**tudy
PIE	**p**rotease **i**nhibitor **e**xperienced [study of Fortovase™ with Kaletra™]
PIVOT	**p**rostate cancer **i**ntervention **v**ersus **o**bservation **t**rial
PLESS	**P**roscar® **l**ong-term **e**fficacy and **s**afety **s**tudy;
PLUS	**p**ropentofylline **l**ong-term **u**se **s**tudy
POEM	**p**atency, **o**utcomes and **e**conomics of **M**IDCAB;
POLAR	**p**ilot study **o**f **l**ow-temperature **a**ngiogenic **r**evascularization; sponsor: CryoCath Technologies, Inc.
POST	**po**sterior **s**troke **t**rial **p**otassium-channel **o**pening **s**troke **t**rial
POWER	**P**TH for **o**steoporotic **w**omen on **e**strogen **r**eplacement [ALX1-11, a recombinant parathyroid hormone (PTH) formulation]; sponsor: NPS Pharmaceuticals
PRAGUE	**pr**imary **a**ngioplasty in patients transferred from **g**eneral community hospitals to specialized PTCA **u**nits with or without **e**mergency thrombolysis
PRAISE	**p**rospective **r**andomized **a**mlod**i**pine **s**urvival **e**valuation
PRECEDENT	**p**rospective **r**andomized **ec**topy **e**valuation on **d**obutamin**e** or **N**atrecor® (nesiritide) **t**herapy; Scios Inc.
PREDICT-HD	neurobiologic **predict**ors of **H**untington **d**isease onset
PREFER	**prefer**ence study of Gengraf™ compared to Neoral™ in stable solid organ transplant subjects
PREPARE	**pre**vent **p**ostmenopausal **A**lzheimer's with **r**eplacement **e**strogens (a.k.a. Alzheimer('s) disease prevention trial)
PRESENT	**pre**liminary **s**afety **e**valuation of **n**anoporous **t**acrolimus-eluting stents; sponsor: JOMED N.V.
PRESTO	**P**arkinson('s) **r**asagiline: **e**fficacy & **s**afety in the **t**reatment of "**O**FF" **p**revention of **res**tenosis with **t**ranilast and its **o**utcomes
PREVENT	**p**revention of **re**current **ven**ous **t**hromboembolism **pr**ogram in **e**x vivo **v**ein graft **en**gineering via **t**ransfection **p**roliferation **re**duction with **v**ascular **en**ergy **t**rial; sponsor: Guidant Corp. **p**rospective **r**andomized **e**valuation of the **v**ascular **e**ffects of **N**orvasc® **t**rial
PRIDE	**pr**otection during saphenous vein graft **i**ntervention to prevent **d**istal **e**mbolization);
PRIME	**pr**amipexole **i**n **m**inority persons with Parkinson('s) disease: **e**fficacy **pr**ogram for **i**rbesartan **m**ortality and morbidity **e**valuations [consists of two studies: IRMA 2 and IDNT]
PRIMO-CABG	**p**exelizumab for **r**eduction in **i**nfarction and **mo**rtality in **c**oronary **a**rtery **b**ypass **g**raft surgery

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

PRINCE	**pr**avastatin **in**flammation/**C**RP **e**valuation
PRINCESS	**p**revention of **rein**farction with early treatment by **c**erivastatin **s**tudy
PRISM-PLUS	**p**latelet **r**eceptor **i**nhibition for ischemic **s**yndrome **m**anagement in **p**atients **l**imited to very **u**nstable **s**igns and symptoms;
PROACT	**pro**lyse in **a**cute **c**erebral **t**hromboembolism
PROACTION	**p**rospective **r**andomized **o**utcomes study of **a**cutely decompensated **c**ongestive heart failure **t**reated **i**nitially in **o**utpatients with **N**atrecor®;
PROBE	**Pr**imacor (milrinone lactate) for **o**ptimization of **b**eta-blocker **e**fficacy
PROBE evaluation	**p**rospective, **r**andomized, **o**pen, **b**linded **e**ndpoint;
PROBIT	**pr**omotion **o**f **b**reastfeeding **i**ntervention **t**rial
PROGENI	**P**arkinson('s) **r**esearch: the **o**rganized **gen**etics **i**nitiative
PROGRESS	**p**erindopril [Aceon®] p**ro**tection a**g**ainst **re**current **s**troke **s**tudy
PROMPT	**p**rofiling **R**emicade **o**nset with **m**ethotrexate in a **p**rospective **t**rial
PROSPER	**pro**spective **s**tudy of **p**ravastatin in the **e**lderly at **r**isk
PROTEKT	**p**rospective **r**esistant **o**rganism **t**racking for th**e** **k**etolide **t**elithromycin [Ketek™]
PROVE IT	**pr**avastatin **o**r ator**v**astatin **e**valuation and **i**nfection **t**herapy;
PROWESS	recombinant human activated **pro**tein C [Xigris™] **w**orldwide **e**valuation in **s**evere **s**epsis
PSYCLOPS	**psy**chosis and **clo**zapine in **P**arkinson's disease
PTAMD	**p**rophylactic **t**reatment of **AMD** [age-related macular degeneration]
PURSUIT	**p**latelet glycoprotein IIb/IIIa in **u**nstable angina: **r**eceptor **s**uppression **u**sing **I**ntegrilin™ **t**herapy
QoLITY	**q**uality **o**f **li**fe **t**rial h**y**pertension;
QUIET	**qu**inapril [Accupril™] **i**schemic **e**vent **t**rial
RACECAR	**r**estenosis **a**nd **c**linical **e**valuation in **c**oronary **ar**teries; sponsor: Medtronic
RALES	**r**andomized **Al**dactone® (spironolactone) **e**valuation **s**tudy for congestive heart failure;
RAPID	**r**adiation **a**fter **P**TA **i**s **d**one; sponsor: Radiance Medical Systems [RDX™ coronary radiation delivery catheter] **r**apid-**a**cting **P**ark**i**nson('s) **d**rug
RAPPORT	**R**eoPro® **a**nd **p**rimary **P**TCA **o**rganization and **r**amdomized **t**rial
RAVEL	**ra**ndomized study with the sirolimus-eluting Bx **Vel**ocity™ balloon-expandable stent [Cypher™]; sponsor: Cordis
REACH	**re**habilitation **a**mong women with **c**oronary **h**eart disease **r**esearch on **e**ndothelin **a**ntagonism in **c**hronic **h**eart failure;
REACT	**r**apid **e**arly **a**ction for **c**oronary **t**reatment; University of Minnesota and JAMA 2000;283:3223-3229 [July 5, 2000]
ReALIZe	**re**search to **a**ssess the **l**ong-term **i**mpact of **Z**omaril™
RECIFE	**re**duction of **c**holesterol in **i**schemia and **f**unction of the **e**ndothelium
REDHOT	**r**apid **e**mergency **d**epartment **h**eart failure **o**utpatient **t**rial [Trial to evaluate clinical utility of the Triage® BNP test in assessing effectiveness of therapy in the management of CHF.]
REGRESS	**re**gression **gr**owth **e**valuation **s**tatin **s**tudy
REIN	**r**amipril **e**fficacy **in** **n**ephropathy
REMATCH	**r**andomized **e**valuation of **m**echanical **a**ssistance **t**herapy as an alternative in **c**ongestive **h**eart failure;
RENAAL	**r**eduction in **e**ndpoints in patients with **n**on–insulin-dependent diabetes mellitus with the **a**ngiotensin II **a**ntagonist **l**osartan

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

RENAISSANCE	**r**andomized **E**nbrel® **N**orth **A**mer**i**can **s**trategy to **s**tudy **an**tagonism of **c**ytokin**e**s
RESPECT	**r**isk **e**valuation and **s**troke **p**revention in the **e**lderly - **c**erivastatin **t**rial;
RESTOR	**R** stent™ **e**fficacy and **s**afety **t**rial **Or**bus; sponsor: Orbus Medical Technologies
RESTORE	**r**andomized **e**fficacy **s**tudy of **t**irofiban for **o**utcomes and **re**stenosis;
REVERSAL	**revers**al of **a**therosclerosis with **L**ipitor™
REVERT	**re**versal of **v**entricular **r**emodeling with **T**oprol-XL®;
RHYTHM	**r**esynchronization for **h**emod**y**namic **t**reatment for **h**eart failure **m**anagement; sponsor: St. Jude Medical [Epic™ HF]
RID-HD	**ri**luzole **d**osing in **H**untington **d**isease
RITZ-2	**r**andomized **i**ntravenous **tez**osentan
ROSTER	**r**otational atherectomy versus ball**o**on angioplasty for diffuse in-**ste**nt **r**estenosis
RUTH	**r**aloxifene **u**se for **t**he **h**eart;
SADHAT	**s**ertraline (Zoloft®) **a**nti**d**epressant **h**eart **a**ttack **t**rial
SADHART	**s**ertraline **a**nti**d**epressant **h**eart **a**ttack **r**andomized **t**rial
SAFE	**s**afety **a**fter **f**ifty **e**valuation
SAFER	**s**aphenous vein graft **a**ngioplasty **f**ree of **e**mboli **r**andomized trial; entry
SAFE-T	**s**otalol and **a**miodarone atrial **f**ibrillation **e**ffectiveness **t**rial
SAGE	**s**tudy **a**ssessing **g**oals in the **e**lderly
SAPPHIRE	**s**ystolic **a**nd **p**ulse **p**ressure **h**emodynamic **i**mprovement by **r**estoring **e**lasticity; sponsor: Alteon Inc. [ALT-711]
SARECCO	**s**tent or **a**ngioplasty after **rec**analization of **c**hronic **c**oronary **o**cclusions
S.A.V.S.	**S**ynercid® as an **a**lternative to **v**ancomycin in **s**taph[ylococcal infections]
SCD-HeFT or SCDHeFT	**s**udden **c**ardiac **d**eath/**h**eart **f**ailure **t**rial
SCRIP	**s**tudy of **c**ardiovascular **r**isk **i**ntervention by **p**harmacists
SCRIPPS	**S**cripps **c**oronary **r**adiation to **i**nhibit **p**roliferation **p**ost **s**tenting
SEAL	**s**imple and **e**ffective **a**rterial c**l**osure study;
SEARCH	**s**tudy of **e**ffectiveness of **a**dditional **r**eductions of **c**holesterol and **h**omocysteine
SECURE	**s**tudy to **e**valuate **c**arotid **u**ltrasound changes in patients treated with **r**amipril [Altace®] and vitamin **E**
SELECT	**sel**enium and vitamin **E** **c**ancer prevention **t**rial; description
SELENA	**s**afety of **e**strogens in **l**upus **e**rythematosus **n**ational **a**ssessment
SHARP	**s**ubcutaneous **h**eparin and **a**ngioplasty **r**estenosis **p**revention
SHELTER	**s**tenting of **h**igh risk patients **e**xtracranial **l**esions **t**rial with **e**mboli **r**emoval;
SHEP	**s**ystolic **h**ypertension in the **e**lderly **p**rogram
SHIPS	**s**tudy of a **h**ome **i**ntervention **p**ost **s**troke
SHOCK	**sh**ould we emergently revascularize **o**ccluded **c**oronaries for cardiogenic shoc**k**
SHOW	**s**tudy of **h**ealth **o**utcomes in **w**eight loss
SICCO	**s**tenting **i**n **c**hronic **c**oronary **o**cclusion
SIESTA	**s**nooze-**i**nduced **e**xcitation of **s**ympathetic **t**riggered **a**ctivity
SILCAAT	**s**tudy of **i**nterleukin-2 (IL-2) in people with **l**ow **C**D4+ T-cell counts on **a**ctive **a**nti-HIV **t**herapy; Chiron Corporation
SILENT	**s**onotherapy for **i**n-**l**esion **e**limination of **n**eointimal **t**issue; sponsor: PharmaSonics Inc.; also see
SILVER	**s**ystolic hypertension **i**nteraction with **l**eft **v**entricular **r**emodeling; sponsor: Alteon Inc. [ALT-711]
SIRIUS	a multicenter randomized double-blind study of the **sir**ol**i**m**us**-coated Bx Velocity™ stent [referred to as Cypher™ sirolimus-eluting stent] in the treatment of patients with de novo coronary artery lesions; sponsor: Cordis

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

SIROCCO	**siro**limus-**c**oated **C**ordis S.M.A.R.T™ nitinol self-expanding stent in the treatment of **o**bstructive superficial femoral artery disease
SMART	**s**econd **m**anifestations of **art**erial disease **s**erum **m**arkers **a**cute myocardial infarction and **r**apid **t**reatment **s**trategies for the **m**anagement of **a**nti**r**etroviral **t**herapy **s**tudy of **m**edicine versus **a**ngioplasty **r**eperfusion **t**rial **s**tudy of **M**icrostent's **a**bility to limit **r**estenosis **t**rial **s**tudy of **m**onoclonal **a**ntibody **r**adioimmuno**t**herapy; **S**ynercid® **m**icrobiological **a**ssessment of **r**esistance **t**rends;
SMILE	**s**urvival of **m**yocardial **i**nfarction **l**ong-term **e**valuation
SNAP	**s**tudy of **n**itroglycerin **a**nd chest **p**ain
SPAF	**s**troke **p**revention in **a**trial **f**ibrillation
SPEED	**s**trategies for **p**atency **e**nhancement in the **e**mergency **d**epartment
SPORT	**s**pine **p**atient **o**outcomes **r**esearch **t**rial **s**tent implantation **po**st **r**otational atherectomy **t**rial
SPORTIF-V	**s**troke **p**revention using **or**al **t**hrombin **i**nhibition in atrial **f**ibrillation - V [5th series of SPORTIF trials];
SOLVD	**s**tudies **of** **l**eft **v**entricular **d**ysfunction
SONIA	**s**troke **o**utcomes and **n**euroimaging of **i**ntracranial **a**therosclerosis
SONORA	**s**afety **o**f **N**eoral **o**utcomes in **r**heumatoid **a**rthritis
S.O.N.O.R.A.[SM]	**s**tudy of **n**ew **o**nset **r**heumatoid **a**rthritis; sponsor: Knoll Pharmaceutical Company
SoS	**s**tent **o**r **s**urgery
SPARCL	**s**troke **p**revention by **a**ggressive **r**eduction in **c**holesterol **l**evels
SPICE	**s**tudy of **p**rotease **i**nhibitor **c**ombination in **E**urope;
SPLASH	**s**onotherapy **p**revention of **l**ate arterial in-**s**tent **h**yperplasia; sponsor: PharmaSonics, Inc.; also see
SPS3	**s**troke **p**revention of **s**mall **s**ubcortical **s**trokes
SSITT	**S**wiss-**S**panish **i**n**t**ermittent **t**rial
SSYLVIA	**s**tenting in **sy**mptomatic atherosclerotic **l**esions of **v**ertebral and **i**ntracranial **a**rteries
STAR	**s**tudy of **t**amoxifen **a**nd **r**aloxifene;
STARS	**s**tandard **t**reatment with **a**ctivase to **r**everse **s**troke
START	**s**aruplase and **t**aprostene **a**cute **r**eocclusion **t**rial **S**t. **T**homas' **a**therosclerosis **r**egression **t**rial **s**tudy of **t**hrombolytic therapy with **a**dditional **r**esponse following **t**aprostene **st**ent versus **a**ngioplasty **r**estenosis **t**rial **st**ent versus directional coronary **a**therectomy **r**andomized **t**rial **st**ents **a**nd **r**adiation **t**herapy; **s**election of **t**hymidine **a**nalog **r**egimen **t**herapy;
STAT	**s**troke **t**reatment with **a**ncrod **t**rial
Stent PAMI	**stent** **p**rimary **a**ngioplasty for **m**yocardial **i**nfarction
STEP-BD	**s**ystematic **t**reatment **e**nhancement **p**rogram for **b**ipolar **d**isorder; study description
STICH	**s**urgical **t**reatment for **i**ntra**c**erebral **h**emorrhage
STOP	**s**onotherapy for the **t**reatment **o**f **p**eripheral vascular disease; sponsor: PharmaSonics, Inc.
STOP-DUB	**s**urgical **t**reatments **o**utcomes **p**roject for **d**ysfunctional **u**terine **b**leeding
STOP-Hypertension	**S**wedish **t**rial in **o**ld **p**atients with hypertension;
STRATAS	**st**udy to determine **R**otablator® **a**nd **t**ransluminal **a**ngioplasty **s**trategy
STRENGTH STRENGTH II	**st**atin **r**esponse **e**xami**n**ed by **g**ene**t**ic **H**AP™ markers; sponsor: Genaissance Pharmaceuticals

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

STRESS	**st**ent **res**tenosis **s**tudy
STRETCH	**s**ymptom, **t**olerability, **r**esponse to **e**xercise **t**rial of **c**andesartan cilexetil [Atacand™] in **h**eart failure
STRIDE	**s**itaxsentan **t**o **r**elieve **i**mpaire**d** **e**xercise in pulmonary hypertension
SUDEP	**s**udden **u**nexpected **d**eath in **e**pile**p**sy
SWEDIC	**Swe**den **di**astolic **c**arvedilol
SWIFT	**s**hould **w**e **i**ntervene **f**ollowing **t**hrombolysis
SWING	**s**ound **w**aves **i**nhibit **n**eointimal **g**rowth; sponsor: PharmaSonics Inc.
SWISS	**s**iblings **w**ith **i**schemic **s**troke **s**tudy
SWOG	**S**outh**w**est **O**ncology **G**roup [an adult cancer clinical trials organization]; SWOG protocols by indication
SYMPHONY	**s**ibrafiban versus aspirin to **y**ield **m**aximum **p**rotection from ischemic **h**eart events post-acute c**o**ro**n**ar**y** syndromes;
SYNERGY	**s**uperior **y**ield of the **n**ew strategy of **e**noxaparin, **r**evascularization, and **gly**coprotein IIb/IIIa inhibitors
TACT	**t**rial to **a**ssess **c**helation **t**herapy [EDTA chelation therapy for coronary artery disease]; sponsor: National Institutes of Health (NIH)
TACTICS	**t**hrombolysis **a**nd **c**ounterpulsation **t**o **i**mprove **c**ardiogenic shock **s**urvival **t**reat angina with **A**ggrastat® and determine **c**osts of **t**herapy with **i**nvasive or **c**onservative **s**trategies [TIMI-18]
TAIST	**t**inzaparin in **a**cute **i**schemic **s**troke **t**rial
TARGET	do **t**irofiban [Aggrastat®] **a**nd **R**eoPro **g**ive similar **e**fficacy outcomes **t**rial
TCAS	**t**emperature **c**ontrol during **a**neurysm **s**urgery
TexCAPS	**Tex**as **c**oronary **a**therosclerosis **p**revention **s**tudy
TeqCES	**Teq**uin® **c**linical **e**xperience **s**tudy
TheraP	**Thera**Source™ **P**d-103 for prevention of restenosis; sponsor: Theragenics Corporation [TheraSource™ intravascular brachytherapy system]
TIGER-PA	**ti**rofiban **g**iven in the **e**mergency **r**oom before **p**rimary **a**ngioplasty
TIME	**t**rial of **i**nvasive vs. **m**edical therapy in **e**lderly patients with chronic CAD
TIMI	**t**hrombolysis **i**n **m**yocardial **i**nfarction; **t**hrombin **i**nhibition in **m**yocardial **i**nfarction
TNT	**t**reating to **n**ew **t**argets
TOAT	**t**he **o**pen **a**rtery **t**rial
TONE	**t**rial **o**f **n**onpharmacologic interventions in the **e**lderly
TOP	**t**reatment of **o**steoporosis with **P**TH [ALX1-11, a recombinant parathyroid hormone (PTH) formulation]; sponsor: NPS Pharmaceuticals
TOPIC	**t**obramycin **o**nce-daily **p**rescribing **i**n **c**ystic fibrosis
TRACE	**tra**ndolapril **c**ardiac **e**valuation study **tr**ial of genetic **a**ssessment in breast **c**anc**e**r
TRAFFIC	**t**he**r**apeutic **a**ngiogenesis with **F**G**F**-2 (fibroblast growth factor) for **i**ntermittent **c**laudication; sponsor: Chiron Corporation
TRANSCEND	**t**elmisartan [Micardis®] **r**andomized **a**ssessme**n**t **s**tudy in a**ce** i**n**tolerant subjects with cardiovascular **d**isease
TREAT	**t**ranilast **re**stenosis following **a**ngioplasty **t**rial
TREND	**t**rial on **r**eversing **en**dothelial **d**ysfunction
TROPHY	**tr**ial f**o**r **p**reventing **hy**pertension;
TRUST	**T**enax® for the prevention of **r**estenosis and acute thrombotic complications. A **u**seful **s**tent **t**rial [Tenax-XR, a silicon carbide-coated stent]; sponsor: Biotronik, Inc.

CLINICAL TRIAL ACRONYMS (NOT ALL INCLUSIVE)

TTT4CNV	**t**ranspupillary **t**hermo**t**herapy **for** **c**horoidal **ne**o**v**ascularization
TURBO	**t**he **u**ltrasound **r**emoval of **b**lood cl**o**ts in vein grafts; Angiosonics
TUSS	**t**uberculosis **u**ltraviolet **s**helter **s**tudy
UK-HEART	**U**nited **K**ingdom **h**eart failure **e**valuation and **a**ssessment of **r**isk **t**rial
UKPDS	**U**nited **K**ingdom **p**erspective **d**iabetes **s**tudy
UNAIDS PETRA	**U**nited **N**ations programme on HIV/ **AIDS** **pe**rinatal **tra**nsmission trial
VA-HIT	**V**eterans **A**dministration **H**DL **i**ntervention **t**rial
Val-HeFT	**val**sartan **he**art **f**ailure **t**rial;
VALIANT	**val**sartan **i**n **a**cute myocardial i**n**farction **t**rial; **V**ascular **A**rchitects femoropop**l**iteal subopt**i**mal **a**ngioplasty aSpire™ ste**n**t **t**rial; sponsor: Vascular Architects
VALUE	**va**lsartan antihypertensive **l**ong-term **u**se **e**valuation;
VANILA	**v**entricular **a**rrhythmia **n**eeding **i**ntravenous **l**idocaine/**a**miodarone
VANQWISH	**V**eterans **A**ffairs **n**on–**Q**-**w**ave **i**nfarction **s**trategies in **h**ospital
VERT	**v**ertebral **e**fficacy with **r**isedronate **t**herapy; risedronate (Actonel®)
VICTORY	electi**v**e and acute stent**i**ng of **c**oronary ar**t**eries **o**n Exp**r**ess™ [coronary stent] s**y**stem; sponsor: Boston Scientific
VIGOR	**Vi**oxx® **g**astrointestinal **o**utcomes **r**esearch
VINTAGE MI	**v**ascular **int**eraction with **age** in **m**yocardial **i**nfarction
VISION	**v**ascular **i**ntervention **s**tudy with **ion**izing radiation; sponsor: Guidant Corp. [Galileo™ intravascular radiotherapy system]
VISP	**v**itamin **i**ntervention for **s**troke **p**revention
VITATOPS	**vita**mins **to** **p**revent **s**troke
VIVA	**V**EGF (vascular endothelial growth factor) in **i**schemia for **v**ascular **a**ngiogenesis
VMAC	**v**asodilation in the **m**anagement of **a**cute **c**ongestive heart failure;
WARCEF	**w**arfarin-**a**spirin **r**educed **c**ardiac **e**jection **f**raction
WARIS-II	**w**arfarin-**a**spirin **rei**nfarction **s**tudy
WARSS	**w**arfarin **a**spirin **r**ecurrent **s**troke **s**tudy
WASID	**w**arfarin-asprin **s**ymptomatic **i**ntracranial **d**isease study
WATCH	**w**arfarin & **a**ntiplatelet **t**herapy in **c**hronic C**HF** **w**omen **a**torvastatin **t**rial on **ch**olesterol
WAVE	**w**omen's **a**ngiographic **v**itamins and **e**strogen trial
WEARIT	**w**earable **c**ardioverter-**d**efibrillator **i**nvestigational **t**rial
WIHS	**w**omen's **i**nteragency **H**IV **s**tudy
WINS	**w**omen’s **i**ntervention **n**utrition **s**tudy
WISE	**w**omen's **i**schemia **s**yndrome **e**valuation;
WIZARD	**w**eekly **i**ntervention with **Z**ithromax® against **a**therosclerosis and **r**elated **d**isorders
Women's HOPE	Women's **h**ealth, **o**steoporosis, **p**rogestin, and **e**strogen study
WRIST	**W**ashington **r**adiation for **i**n-**s**tent restenosis **t**rial
XISHF	**x**amoterol **i**n **s**evere **h**eart **f**ailure
X-TRACT	X-Sizer™ for **tr**eatment of thrombus and **a**therosclerosis in **c**oronary interventions **t**rial
ZEUS	**Z**omaril™ **e**fficacy/**u**tility and **s**afety;
ZIPP	**Z**oladex® (goserelin acetate implant) **i**n **p**remenopausal **p**atients